TITLE

"PEPTIDE TURN MIMETICS"

FIELD OF THE INVENTION

THIS INVENTION relates to new compounds designed to be peptide turn mimetics, and to new compounds useful for the synthesis of peptide mimetics, especially turn mimetics. Peptide mimetics are used to reproduce the important structural and functional elements contained in a bio-active peptide sequence principally in order to develop novel pharmaceuticals with increased binding affinity, selectivity, stability and/or oral bioavailability compared to the bio-active peptide.

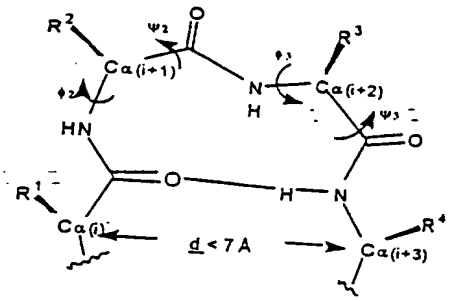
BACKGROUND OF THE INVENTION

Reverse turns (beta and gamma turns and beta bulges) are localised on the protein surface (Kuntz, 1972) and are of importance in protein interactions (Rose *et al.*, 1985; Chalmers and Marshall, 1995) (and references contained therein). In addition reverse turns are important structures of peptide hormones and other biologically active peptides and cyclic peptides.(Giannis and Kolter, 1993; Olson *et al.*, 1993; Kessler *et al.*, 1995)

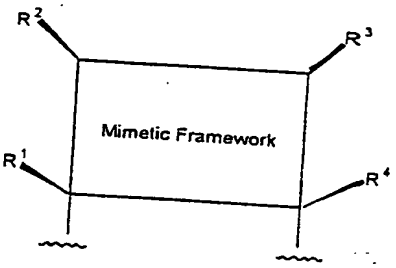
Peptide mimetics and peptide turn mimetics have as their object the replacement of a peptide sequence (a peptide turn) with a new compound which retains the elements essential for biological activity, thereby enabling or facilitating the development of novel pharmaceuticals devoid of the inherent problems of peptides - namely flexibility and poor pharmacodynamics. The essential elements for biological activity are thought to be the peptide sidechain groups (Farmer and Ariëns, 1982: Ball and Alewood, 1990), therefore a peptide mimetic should include the side chain groups to have the best chance of retaining biological activity. A peptide mimetic may then take the form of a framework for displaying sidechain groups in an appropriate arrangement.

The majority of reverse turns are beta turns. The generally accepted definition of the beta turn is a sequence of four residues where the distance between the alpha carbons of residue (i) and residue (i+3)

(defined as d) is less than 7Å, and the central residues (i+1, i+2) are non-helical.(Lewis *et al.*, 1973) The general structure is shown below and includes the phi (ϕ) and psi (ψ) backbone dihedral angles that are used to describe the conformation of the peptide backbone. A schematic conversion of the beta turn to a beta turn mimetic is also shown - the peptide backbone is here replaced by an undefined framework.

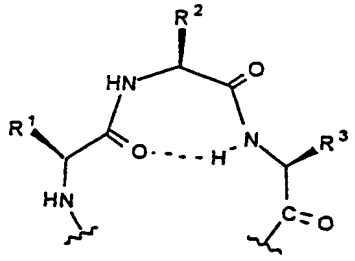


General structure of a hydrogen bonded β-turn. The four backbone dihedral angles traditionally used in turn classification are indicated, and also the position of the 7Å upper distance cutoff for d used for the definition of β-turns.



A schematic representation of a beta turn mimetic - the peptide backbone has been replaced by an alternative chemical framework, represented here by a rectangle

The gamma turn is generally defined by the presence of a hydrogen bond between C=O (*i*) and N-H (i+2) to form a pseudo seven membered ring as illustrated below (Milner-White, 1988). Where the equivalent hydrogen bond is present in a beta turn a pseudo ten membered ring is formed.



General structure of a γ-turn, defined by the presence of a hydrogen bond between the C=O of the (i) residue and the N-H of the (i+2) residue, as indicated.

The chemical synthesis of a framework having four independent chiral groups each with a wide range of possible functionality (for example, a beta turn mimetic) is a very significant synthetic challenge (Nakanishi and Kahn, 1996) as illustrated by the the fact that most proposed beta turn mimetics either do not provide for the incorporation of any sidechain functionality, or provide for a limited range of functionality, and at a limited number of positions. Reference may be made to reviews by Ball and by Hölzemann for illustration of these points (Ball and Alewood, 1990; Hölzemann, 1991; Hölzemann, 1991). In the case of mimetics that do provide for the incorporation of sidechain functionality, the syntheses are often complex and lengthy, and most seriously may require a different synthetic method for different sidechain sequences (i.e. the synthetic method is not generic). For example, in the work of Callahan, Huffman and Newlander on gamma turn mimetics the synthetic method varied depending on the sidechain sequence required - a 10 step sequence for a Gly-Phe-Leu mimetic, 13 steps for Phe-Gly-Val and 21 steps for Ala-Phe-Ala (Huffman *et al.*, 1988; Callahan *et al.*, 1992; Newlander *et al.*,1993). Given that the possible combinations of three residue sequences of the 20 natural amino acids is 8000 (20x20x20), and 160,000 for the four residue beta turn sequence, such non-generic methods are of limited use. The methods of Callahan and Huffman were further hampered by a lack of chiral control, as are most methods in the art.

In the development of peptide turn mimetics a further important issue is the reproduction of the variety of different turn conformations, particularly of the beta turn. Several different methods of describing turn conformation have been proposed, the traditional method having several turn types based on the backbone dihedral angles of the (i+1) and (i+2) residues i.e. I, I', II, II', III, III', IV, V, VIa, VIb, VII and VIII, with even this diversity of types being insufficient to adequately describe turn conformations.(Richardson, 1981; Wilmont and Thornton, 1990; Ball

et al., 1993) No *single* mimetic framework can accurately mimic this diversity of turns; a selection of mimetic frameworks is required.

The problems encountered in the development of peptide turn mimetic syntheses are discussed in a review by Kahn (Kahn, 1993) and reference may also be made to a review article entitled "Design of Peptidomimetics" (Nakanishi and Kahn, 1996) which discusses aspects of mimetic design and developments regarding peptide mimetics.

The uses of reverse turn mimetics (and peptides or other compounds containing reverse turn mimetics) in drug development have been described in the art, notably in publications by Kahn and co-workers (Kahn, 1996; Nakanishi and Kahn, 1996; Qabar *et al.*,1996) and references contained therein. An important example of the application of reverse turn mimetics is the production of mimetics of known biologically active cyclic peptides (typically penta- or hexapeptides), as illustrated by Hirschmann and co-workers with □-D-glucose based mimetics.(Hirschmann *et al.*,1992; Hirschmann *et al.*, 1993)

Other beta turn mimetics having biological activity are known in the art. For example, U.S. Patent 4535169 discloses a method for the synthesis of beta turn mimetics which can incorporate a functional substitution for the (i+3) sidechain (only), and Krystenansky *et al.* disclose a leucine enkephalin mimetic based on this method which had analgesic activity one third the potency of morphine (Krstenansky *et al.*, 1982).

Reference may also be made to U.S. Patents 5475085 and 5618914 and International Publication WO96/22304 (all Kahn, M) which describe methods for the synthesis of a range of reverse turn mimetics. These mimetics are all produced by a modular synthesis technique (that may be applied to solid phase synthesis) which involves amino acid derivatives and various dipeptide azetidinones synthesised by a variety of techniques. An important common step in all of the syntheses of these mimetics is the cyclisation reaction which involves the azetidinone as activated ester component. Conformational variation is introduced to these mimetics by the inclusion of a variable component ("X") in the ring

of the cyclic turn mimetics. It should be noted that with two exceptions (the parent mimetics which have X=NH and have a ten or eleven membered ring) the beta turn mimetics produced by these methods have ring sizes of twelve members and above. Such large rings allow many conformations with d>7Å, the mimetic conformations are therefore biased away from the accepted definition of a beta turn (d less than 7Å), or more importantly the conformations are biased away from the most common reverse turn conformations which have d in the range of 4.5Å to 6Å (Rose *et al.*, 1985; Gardner *et al.*,1993). Enkephalin mimetics have been made (Gardner *et al.*, 1993) and also mimetics of a loop of CD4 that inhibit binding of HIV gp120 and infection of human lymphocytes (Chen *et al.*, 1992). The synthetic methods described for the majority of these mimetics appear to be limited with respect to the possible functionality at the (i) and (i+1) positions, and indeed no mimetic with any functionality at the (i+1) position (other than -H = glycine = no sidechain) appears to have been described at this time.

Reference may also be made to International Publication WO97/15577 (Kahn, M) which describes the synthesis of bicyclic reverse turn mimetics and chemical libraries containing such reverse turn mimetics. While concise, the synthetic methods do not provide for control of chirality at all positions, and the degree of sidechain function generality is questionable at two of the four positions. Furthermore the structure of the mimetics means they are not able to be easily incorporated in a peptide sequence, nor do they reproduce the relative positioning of the sidechain groups in the ideal manner (each sidechain attachment position should ideally be separated by three covalent bonds, as in a peptide).

Reference may also be made to the turn mimetics of Virgilio *et al.* (Valle *et al.*, 1989; Virgilio and Ellman, 1994; Virgilio *et al.*, 1996) that incorporate functionality at the (i+1), (i+2) and (i+3) positions (but not the (i) position), and that do not allow for incorporation of the mimetic in a peptide sequence (i.e. no amino and carboxy terminal groups in addition to the sidechains are present).

Reference may be made to U.S. Patents 5438188 and 5470849 (Callahan and Huffman) that describe biologically active compounds containing gamma turn mimetics, providing further illustration of the general utility of reverse turn mimetics.

Reference may also be made to International Publication WO95/25120 that describes the use of turn mimetics in the synthesis of peptide vaccines for generating a protective immune response in warm blooded animals.

In the methods and mimetics of the aforementioned references several common problems are evident: limited numbers of sidechains are able to be reproduced, there is limited control of chirality in the syntheses and a limited range of sidechain functions could be included. In addition, many of the syntheses of turn mimetics described are relatively long and complex, even when not all the sidechain functions are included, for example the syntheses of certain enkephalin mimetics were in the range of approximately 15 to 21 steps (Gardner *et al.*, 1993). There is therefore still a need in the art for peptide mimetics that can incorporate a wide range of sidechain functions in all positions, that can be readily synthesised with control of chirality, and that have a wide range of conformations corresponding to those found in native peptides.

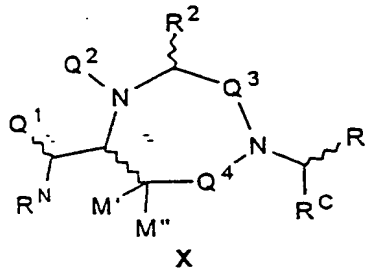
OBJECT OF THE INVENTION

It is the object of the invention to provide novel compounds useful as, and useful for the synthesis of, conformationally constrained mimetics of biologically active peptides and proteins (peptide mimetics). In particular, the invention provides new compounds and methods for the synthesis of new peptide reverse turn mimetics that can display a wide range of sidechain functions at all sidechain positions, can be incorporated in a peptide sequence, can be readily synthesised, and have a variety of conformations.

SUMMARY OF THE INVENTION

This invention describes novel compounds useful for the synthesis of peptide mirnetics, and describes the use of these compounds

for the synthesis of novel reverse turn mimetics. The reverse turn mimetics of the invention have the general structure **X**, or in a preferred embodiment the general structures **I-VI** (which are subsets of the general structure **X**; see below and Figures 1 and 2 on the attached sheets; the structures are fully described in the detailed description following this summary).



X

It has now been discovered that B-allyldialkylboranes (e.g. **Rg1a-i**, Figure 3) react with imines 3 (Scheme 1) to give the novel allyl amines **4a-d** in good yield and with a very high degree of chemo- and stereoselectivity. This is surprising because in contrast to these good results, allylation with the related B-allyldialkoxyboranes (e.g. **Rg1j**, Figure 3) or allylcopper or allylzinc reagents gave inferior results with racemisation and reaction at other functional groups. The reaction of imines **3** to form compounds **4a-d** and formation of the related compounds **5-8a-d** (all of which are made from compounds **4a-d**) forms the basis of the synthesis of all the compounds of the invention, and hence the invention. Thus the allyl amines **4a-d** are suprisingly valuable intermediates for the synthesis of new peptide mimetics, particularly reverse turn mimetics, enabling the synthesis of the significant variety of new reverse turn mimetics of the invention (having the general structure **X**), by the variety of different pathways described herein. All the mimetic systems of the invention can be incorporated into peptide sequences (i.e. they include amino and carboxy termini in addition to the sidechain

functions), or if desired the amino and/or carboxy termini can be omitted from the mimetic.

As described above, there is a need for a wide range of different mimetics to better reproduce the wide range of conformations found in native reverse turns. The turn mimetics of the invention have a large variety of novel functionalised ring structures, each of these therefore having novel conformational characteristics. Furthermore, the structure and ring sizes of many of the turn mimetics make them well suited to the reproduction of the geometry of the more common native reverse turn conformations (those having d of 4.5Å to 6Å).

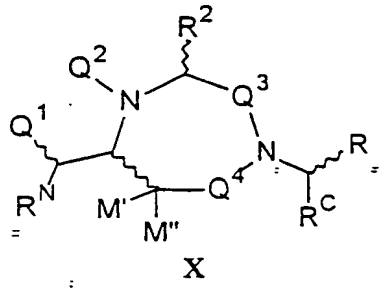
The synthetic methods described in this invention are generally superior to the prior art in terms of the capacity to include a wide range of side chain functions, in all the sidechain positions, without significant changes in the synthetic method; that is, the methods are more truly *generic*. In addition, the control of chirality in the synthesis of the mimetics of the invention is superior to the prior art - an important consideration in the elucidation of structure-activity relationships and the development of novel pharmaceuticals, and other commercially useful peptide mimetics, as diastereomeric mixtures are normally unsuitable and may be impractical or impossible to separate on a commercial basis. Furthermore, selective access to a range of different diastereomers for a particular mimetic with a given sequence provides a selection of different conformations. Thus in a mimetic with four chiral centres there are a total of 16 (2^4) possible diastereomers - each having a different conformation. The methods of the invention allow for a high level of chiral control by using available chiral starting materials, non-racemising conditions and diastereoselective reactions.

The invention includes all novel intermediates used in the preparation of the turn mimetics and more generally useful for the preparation of peptide mimetics, particularly **4-8(a-d)**, Scheme 1 and **10**, Scheme 2. Also **11-12**, Scheme 3; **13-14**, Scheme 4; **16-17**, Scheme 5; **18-19**, Scheme 6; **21-22**, Scheme 7; **23(a-d)-25(a-d)**, **26**, Scheme 8; **27-**

28, Scheme 11; **29-34**, Scheme 12; **35(a-c)**, **36-38**, Scheme 13; **43-46**, Scheme 15.

DETAILED DESCRIPTION OF THE INVENTION

The peptide mimetics of this invention have the general structure **X**, shown below and defined as follows:-



X

wherein R and R^2 and other R groups referred to hereinafter inclusive of R^1, R^3, R^4, R^{n+3} and R^{n+4} etc. unless otherwise indicated, are amino acid side chain groups, each independently chosen and therefore the same or different (two separate R groups in the same mimetic do not require a different suffix to indicate that they are independently chosen and can be the same or different). The definition of "amino acid side chain group" as used in this document is the same as the definition of "amino acid side chain moiety or derivative" as described in International Publication WO97/15577, pages 7-9 (Kahn, M), incorporated herein by reference. Amino acid side chain groups typically correspond to, but are not limited to, those found in natural amino acids and derivatives and in common unnatural amino acids. Thus for glycine R = hydrogen; for alanine R = methyl; for phenylalanine R = $-CH_2Ph$; for homophenylalanine R = $-CH_2CH_2Ph$; for valine R = $-CH(CH_3)_2$; for leucine R = $-CH_2CH(CH_3)_2$; p-nitrophenylalanine R = $-CH_2((4\text{-}NO_2)Ph)$; naphthylalanine R = $-CH_2$-naphthyl etc. Also included are cyclic amino acid sidechains such as for proline, hydroxyproline and homoproline which involve a cyclization to the adjcent backbone nitrogen atom or the equivalent position, but only where this is possible (i.e. the amine or

equivalent atom is not already substituted as part of the heterocyclic mimetic framework).

Z is normally hydrogen, methyl, ethyl, formyl or acetyl, and may alternatively be R or $-CH_2R$ or -C(O)R where R is an amino acid side chain group, or alternatively Z is part of a cyclic amino acid side chain group joined to R^2 (for example to mimic a proline residue at position (i+1)). For **II(i)** referred to hereinafter, Z cannot be hydrogen due to compound instability.

R^C is the carboxy terminal part of the mimetic, typically $-C(O)Pg^C$ or alternatively hydrogen or an amino acid side chain group R or $-CH_2R$.

Pg^C (and $Pg^{C'}$ etc.) is a protecting group for carboxylic acid, typically including, but not limited to: alkoxy, benzyloxy, allyloxy, fluorenyl methyloxy, amines forming easily removable amides, or alternatively an appropriate cleavable linker to a solid phase support, or such a support itself, or alternatively hydroxy –OR, -NHR or remaining C-terminal portion of the mimetic system as described below.

R^N is the amino terminal part of the mimetic, i.e. $-N(Z')Pg^N$,

Z' is normally hydrogen, alternatively methyl (to mimic an N-methyl amino acid residue at position (i)), or alternatively part of a cyclic amino acid side chain group joined to R^1 (for example, to mimic a proline residue at position (i)).

Pg^N (and $Pg^{N'}$) is a protecting group for amine, typically including, but not limited to: Boc, Cbz, Fmoc, Alloc, trityl; or alternatively an appropriate cleavable linker to a solid phase support, or such a support itself, or alternatively hydrogen or R or -C(O)R where R is an amino acid side chain group, or alternatively part or all of the remaining N-terminal portion of the mimetic system, as described below.

M', M'' are normally hydrogen, alternatively one or more may be C_1-C_4 alkyl (preferred methyl), chloro, C_1-C_4 alkoxy (preferred methoxy).

$Q^1 = R^1$ and $Q^2 = Z$; alternatively there is a cyclisation from Q^1 to Q^2 and then in preferred embodiments of the invention Q^1Q^2 = CH(R)C(O) or $-CH_2CH(R)C(O)-$ or $-CH_2CH_2CH(R)C(O)-$. Q^1Q^2 can also be: $-CH(R)CH_2-$ or $-CH_2CH(R)CH_2-$ or $-CH_2CH_2CH(R)CH_2-$ or $-CH_2CH(R)-$ or $-CH_2CH_2CH(R)-$ or $-CH(R)CH_2CH_2-$ or $-CH_2CH(R)CH_2CH_2-$ or $-CH(R)CH_2C(O)-$ or $-CH_2CH(R)CH_2C(O)-$.

Q^5 = hydrogen, C_1-C_4 alkyl, chloro or C_1-C_4 alkoxy and Q^3 = Y or $-C(O)NHCH(R)Y-$ or $-C(O)ENHCH(R)Y-$; or alternatively when $Q^3 = -C(O)N(Q^5)CH(R)Y-$ Q^5 is a covalent bond from the Q^4 group to the nitrogen atom in Q^3 (a cyclisation-forming a bicyclic ring system).

Y is selected from the group consisting of C(O) and CH_2 and Q^4 is selected from the group consisting of CHM^I, C(O), $CH(Q^5)CH_2$ and $CH(Q^5)C(O)$ with the provisos that:

(i) $Q^4 = CH(M^I)$, Y is C(O);

(ii) Q^4 = C(O), Y is CH_2;

(iii) $Q^4 = CH(Q^5)CH_2$, Y is C(O); and

(iv) $Q^4 = CH(Q^5)C(O)$, Y is CH_2.

$E=-(AA)_n-$ where n = 1, 2, 3, 4... (n = 1 to about 300, but more typically n is between 1 and 30) and AA is an amino acid residue (e.g. AA = $-NHCH(CH_3)C(O)-$ for alanine); E is therefore a loop of n amino acids which are linked in a cycle by the rest of the mimetic system. The loop may also incorporate non-alpha amino acids, alpha dialkyl amino acids or any other amino acid which confers favourable properties on the mimetic system, for example increased binding affinity, or ease of detection, identification or purification. The invention, when used with such larger loops, is functioning as a covalent hydrogen bond mimic (another aspect of the invention), as generally described by Arrhenius *et al.* (Arrhenius *et al.*, 1987) and also in U.S. Patent 5807979 (Arrhenius *et al.*).

Preferred embodiments of the invention are the structures I-VI, as illustrated in Figures 1 and 2 and defined in Table 1:-

Table 1

Mimetic	Q^1	Q^2	Q^3	Q^5
I	R^1	Z	Y	-
II	R^1	Z	-C(O)NHCH(R)Y-	M^l
III	R^1	Z	-C(O)NHCH(R)C(O)-NHCH(R)Y-	M^l
IV	R^1	Z	$-C(O)N(Q^5)CH(R)Y-$	Q^3
V	$-CH(R)C(O)Q^2$	Q^1	Y	M^l
VI	$-CH_2CH(R)C(O)Q^2$	Q^1	Y	M^l

Recursive entries of Q groups in Table 2 indicate a cyclisation - thus mimetics V and VI have a cyclisation between Q^1 and Q^2, and mimetic IV has a cyclisation between Q^3 and Q^5. In the Tables, the groups Q^1-Q^5 and Y are as defined above, and the other groups are asdefined herein.

The compounds of this invention have been designed to allow for incorporation in a peptide or protein chain, or for covalent attachment to any molecule or group that may be useful for the enhancement of the biological activity, or other property, of the peptide mimetic. Thus the mimetics typically contain amino and carboxy termini independent of the sidechain functions. The term "remaining C- (or N-)

terminal portion of the mimetic" is any group, molecule, linker, support, peptide, protein, nucleoside, glycoside or combination of these, covalently linked to the mimetic. Typically such remaining portions would be peptides or combinations of peptides and other mimetics, or compounds to facilitate detection or identification, or to improve the pharmacodynamics or other useful feature of the mimetic system.

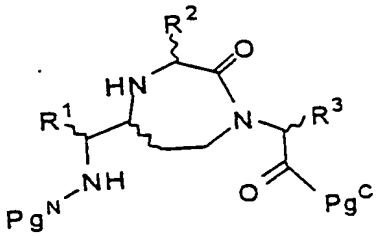
In addition, any R group (an amino acid side chain group) may serve as an attachment point to a solid support, or to a linker to a solid support, or as a covalent attachment point for another molecule that may be useful for the enhancement of the biological activity, or other property, of the mimetic, as described above for the remaining C- or N-terminal portions of the mimetic.

The term "cleavable linker" and "solid phase support" are as defined in International Publication WO97/1557

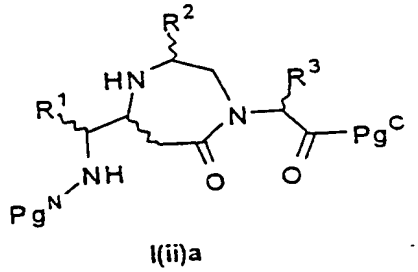
The use of a wavy line for one of the bonds at a chiral centre in the general structures **X** and **I-VI** and in the other structures in the Figures and Schemes indicates that the centre may be in either the (R) or (S) configuration, or be a mixture in any proportion of the (R) and (S) configurations. In most circumstances it is preferable to avoid mixtures of configurations unless the intention is to provide a mixture of diastereomers for example for the purpose of more efficient screening (by the use of a mixture) or for synthetic expediency. Chirality at the amino acid side chain positions in the compounds of the invention (e.g. at R^1 to R^4) is controlled by the use of chiral starting materials (L or D amino acids) and the avoidance of synthetic conditions which cause racemisation. The configuration at chiral centres formed in the mimetic synthesis is dependent on several factors and can be controlled in several cases, but in other cases mixtures of diastereomers will result, which can potentially be separated by physical means. A significant advantage of the invention is the superior level of chiral control possible at the chiral centres in the mimetics.

EXAMPLES OF PREFERRED EMBODIMENTS OF THE MIMETICS

□-Turn mimetics **I(i)a**, **I(ii)a** (M, M', M'', Z and Z' = hydrogen):

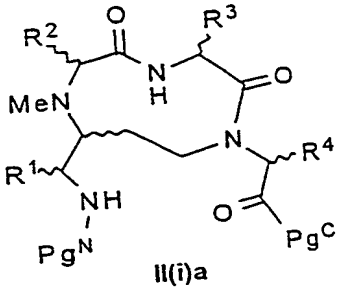


I(i)a

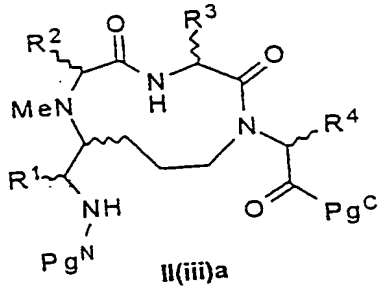


I(ii)a

□-Turn mimetics **II(i)a**, **II(iii)a** (M, M', M'' and Z' = hydrogen, Z = Me):

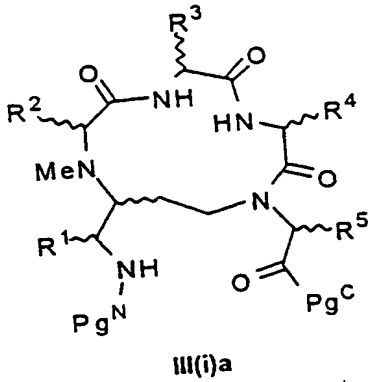


II(i)a

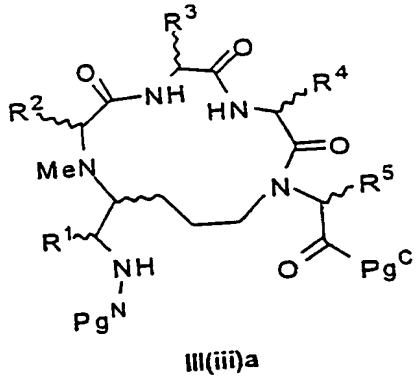


II(iii)a

□-Bulge mimetics **III(i)a**, **III(iii)a** (M, M', M'' and Z' = hydrogen, Z = Me):

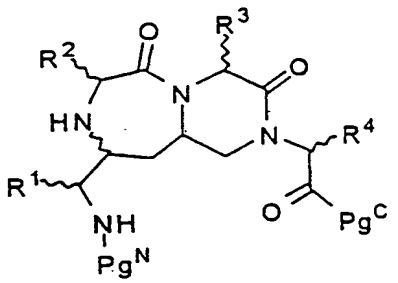


III(i)a

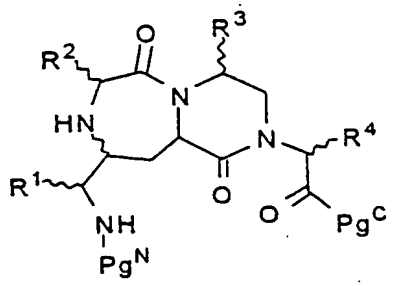


III(iii)a

Bicyclic □-turn mimetics IV(i)a, IV(ii)a (M, M', M'', Z and Z' = hydrogen):

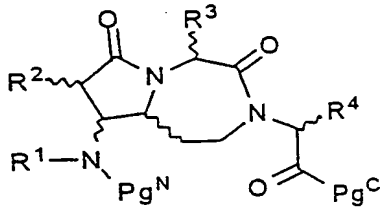


IV(i)a

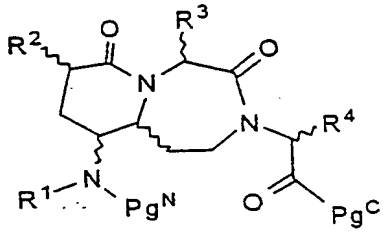


IV(ii)a

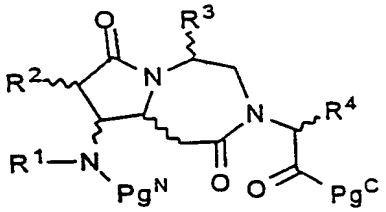
Bicyclic □-turn mimetics V(i)a, VI(i)a, V(ii)a, VI(ii)a (M, M'and M'' = hydrogen):



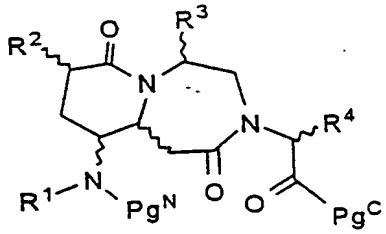
V(i)a



VI(i)a



V(ii)a

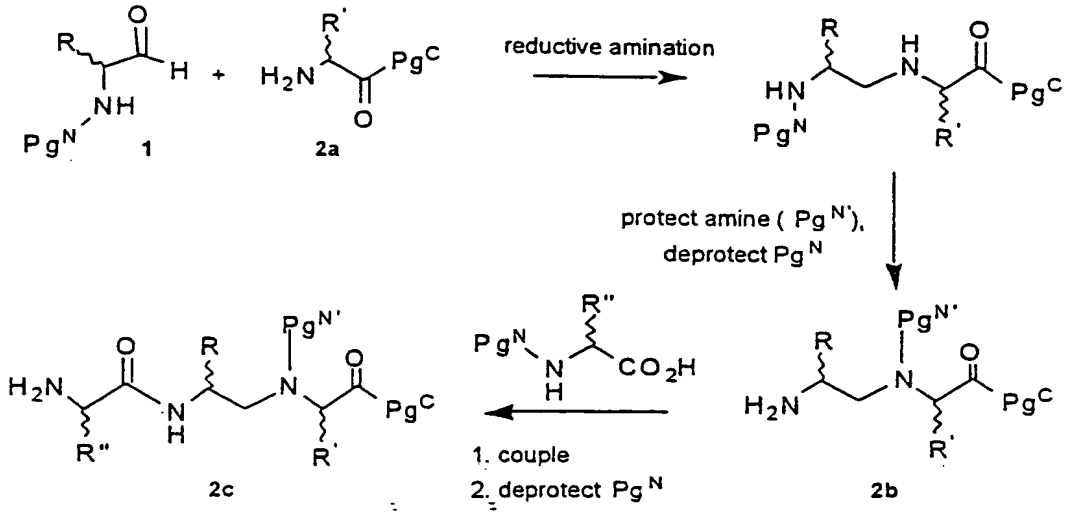


VI(ii)a

The synthesis of all the mimetics described in this specification may proceed initially by the same general synthetic procedure for formation of the common intermediates - reaction of imines **3** with allyl metal reagents **Rg1** (allyl boranes preferred) to give the allyl diamines **4**, which are new, as described in Scheme 1. The other compounds of Scheme 1 (i.e. **5-8**) may all be derived from the allyl diamines **4**, as described in Scheme 1 and in the comments below. The

allylation reaction of imines **3**, which falls within the scope of the invention, is remarkable for its mildness and selectivity - allowing a wide range of functional groups to be present in the rest of the molecule, a very important consideration in the synthesis of peptide mimetics. Another important feature of the reaction of allylboranes with the imines **3** is that it proceeds in good yield (e.g. >50% isolated yield) in the sterically hindered general case where R^1 and R^2 are both not hydrogen - i.e. for all mimetics of dipeptides not containing glycine. Scheme 1 and all subsequent Schemes describe the preferred case of R^N=NHPg^N and R^C=C(O)Pg^C (Figures 1 and 2), analogous methods apply in the general case.

In relation to Scheme 1, preparation of the imines **3** is completed by condensation of an amino acid aldehyde (compound **1**) with an amine (**2a-d**). The aldehydes **1** may be prepared by either oxidative procedures from the corresponding N-protected amino alcohol, or reduction of an N-protected amino acid derivative (Fehrentz and Castro, 1983), the different approaches have been reviewed, (Jurczak and Golebiowski, 1989) (see also Goel *et al.*, 1988, *Org. Syn.* **67** 69). The amines **2a** are amino acid esters (or other acid protected amino acid derivatives), which are commercially available or may be synthesised by standard procedures from amino acids. Amines **2b-2d** are prepared by reductive amination of an amine **2a** and an amino acid aldehyde **1**:



Amines **2d** are prepared by repeated coupling/deprotection steps (as in conversion of **2b** to **2c**), standard techniques of peptide synthesis.

The reductive amination procedure for the alkylation of amines by aldehydes is well established in the art. (See for example, Sasaki and Coy, 1987, Peptides **8** 119), the preferred reagents are sodium cyanoborohydride (Borch *et al.*, 1971; Hutchins and Natale, 1979; Gribble and Nutatits, 1985), or more preferred sodium triacetoxyborohydride in dichloroethane. (Abdel-Magid *et al.*, 1996).

Methods for the formation of amide bonds (coupling) are well established in the art. For coupling at more hindered amines the use of certain reagents, for example those based on 1-hydroxy-7-azabenzotriazole (Ehrlich *et al.*, 1993; Carpino *et al.*, 1994), or the use of amino acid fluorides (Carpino *et al.*, 1990; Wenschuh *et al.*, 1994) is advantageous.

Protecting strategies for the synthesis of peptides and peptide mimetics are well established in the art, for example a five dimensional orthogonal strategy was used by Hirschmann and co-workers in the synthesis of a somatostatin mimetic.(Hirschmann *et al.*, 1996) A more general reference work on protection/deprotection is the monograph by Greene and Wuts.(Greene and Wuts, 1991).

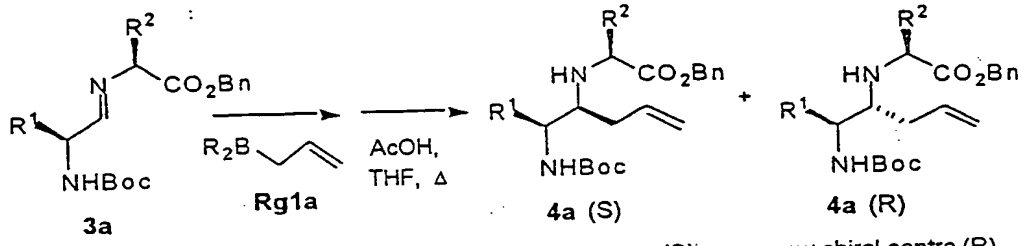
The example syntheses described in this document use solution phase chemistry. The mimetics may also be synthesised by analogous solid phase techniques, or by a combination of solid phase and solution phase techniques, or the mimetics may be incorporated in normal solid phase peptide synthesis in the same way as a standard protected amino acid derivative. A review by Früchtel and Jung (Früchtel and Jung, 1996) details the state of the art in solid phase organic synthesis (in 1996).

It will be clear to those skilled in the art that the mimetics of the invention, due to their generic methods of synthesis, are suited to the application combinatorial chemistry techniques (more specifically combinatorial organic synthesis) and certain associated identification and screening techniques. The application of combinatorial and associated technologies to drug discovery are well known in the art and have been reviewed, see for example papers by Gallop *et al.* and by Gordon *et al.*, and references therein, incorporated herein by reference (Gallop *et al.*, 1994; Gordon *et al.*, 1994). Additionally, reference may be made to a review by Thompson and Ellman on the synthesis and application of small molecule libraries, and references therein, incorporated herein by reference.(Thompson and Ellman, 1996).

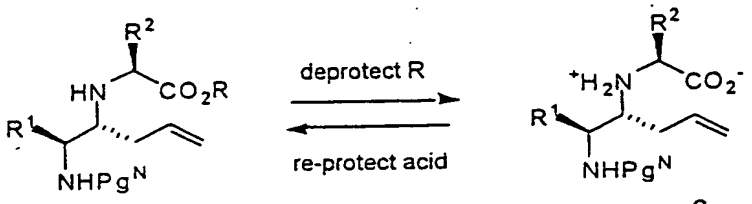
The imines **3** form rapidly at room temperature on mixing of the amine and aldehyde in an appropriate solvent, e.g. CH_2Cl_2 or diethyl ether, with liberation of water. The water is removed with a drying agent, e.g. dried $MgSO_4$, which is subsequently removed by filtration. The imines are then reacted with an allyl metal reagent (**Rg1**) to give, after work-up, compounds **4** (Scheme 1).

In relation to reagents **Rg1**: standard allyl organometals, such as allyl magnesium bromide, are unsuitable for reaction with imines **3** due to a lack of selectivity for the imine function over the carboxylic acid derived groups (esters, amides) also present in **3**. Allyl copper and zinc reagents have been used in selective reactions with imines (Bocoum *et al.*, 1991; Basile *et al.*, 1994) but in the case of imines **3** these reagents

result in extensive racemisation at the □-imine chiral centre, and attack esters present in the imine to a significant extent. While some of the desired target **4** may be produced by many allyl metal reagents on reaction with **3**, the reaction product typically contains a mixture of four diastereomers and also by-products from reaction at the carboxylic acid derived groups (especially esters). In contrast to these results, reaction of the imines **3** with allyl boranes, such as B-allyl-9-borabicyclo[3.3.1]nonane (allyl-9-BBN), **Rg1a**, gives excellent results and reasonable diastereoselectivity (>50% isolated yield based on crude aldehyde, and ~80:20 diastereoselectivity where R^1 is not H).



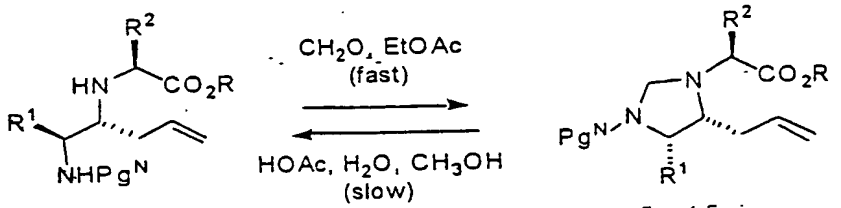
By the use of allyl trialkylboranes with appropriate chiral alkyl groups such as B-allyl-diisopinocampheylborane (allyl-DIP, **Rg1b** and **Rg1c**), or the diisocaranylboranes **Rg1d-e** it is possible to produce give only the major product (one diastereomer, >99:1) in good yield and purity. The configuration at the new stereocentre was determined to be (R) when using aldehyde derived from natural (S) configuration amino acids, and the stereocontrol exerted by the □-aldehyde chiral centre was dominant over the effect of chiral boron ligands and over the effect of the other amino acid chirality in all cases examined. The (+)DIP reagent **Rg1b** gave higher diastereoselectivity on imines derived from natural (S) configuration aldehydes than **Rg1c** (from (-)DIP). The purity of the allylation products **4a** may also be improved by the removal of the ester protecting group Pg^C to give a crystalline amino acid which can be recrystallised (e.g. from ethanol/water) to the desired level of purity and then reprotected.



4a (R) **4a** (R), Pg ^{C}=H crystalline derivative

The use of crotyl (**Rg1f**, **Rg1h-i**), methallyl (**Rg1g**) or other substituted allyl derivatives leads to bridge substituted mimetics (mimetics where at least one of M, M' and M" is not hydrogen) with further opportunities for stereocontrol. The less reactive allyl boronate allyldimethoxyboron (**Rg1j**) was found to give inferior results (significant epimerisation at C□(i)) compared to the allyltrialkylboranes. Many allylboronate and related reagents (e.g. **Rg1k-m**) are described in the literature, and some of these may be more effective than allyldimethoxyboron for the conversion of **3** to **4**. Selective reactions using allylic metals have been reviewed by Yamamoto and Asao, Tables IV and V in the review (pp 2224-2230) list a wide variety of allyl boron reagents.(Yamamoto and Asao, 1993) The preparation of allyl-9-BBN and other allyltrialkylboranes has been described by Brown and coworkers (Kramer and Brown, 1977; Brown and Jadhav, 1983; Brown and Jadhav, 1984; Brown and Bhat, 1986; Brown, Randad *et al.*, 1990) Allyltrialkylboranes may also be prepared by the reaction of the corresponding B-chloro or B-methoxy derivative with an allylmagnesium bromide (-78_C, diethyl ether), and reacted in situ with the imine (Yamamoto and Asao, 1993). The imines **3** formed from two non-glycine derivatives (i.e. R^1 and R^2 not H) are significantly hindered about the imine nitrogen, and the use of bulky boron ligands (such as diisopinocampheyl) can reduce the reaction yield. For high yield and selectivity smaller chiral B-allyl compounds, e.g. those based on 2,5-dimethylboracyclopentane are preferred (e.g. **Rg1n**, Figure 3).

In relation to protection and deprotection of compounds **4** and **5**: addition of formaldehyde solution to **4** results in the rapid formation of imidazolidines **5**; the relative configuration in the major allylation products **4** results in a 4,5-cis-substituted imidazolidine **5**. This protection strategy is important for further reaction of these compounds. The protecting group is removed by treatment with aqueous acid (e.g. aqueous methanolic acetic acid).

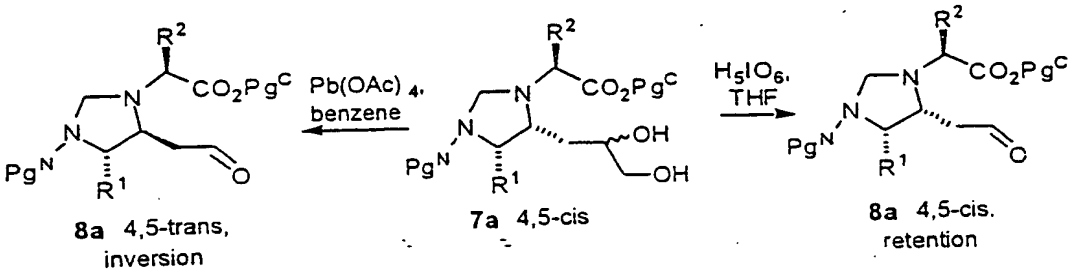


4a (R) **5a** 4,5-cis

A similar protection system is the dibenzyltriazone group of Knapp and co-workers,(Knapp *et al.*, 1992) the paper describes other deprotection conditions and is incorporated herein by reference. An alternative deprotection method involves the hydrogenation of the imidazolidine system to an amine N-methyl group (40psi H_2, Pd-C, MeOH, 48hrs), a conversion that can be used to give mimetics where Z = Me.

In relation to oxidation of alkenes **5**: acids **6** can be synthesised directly by oxidative cleavage of the alkenes **5**, e.g. by $RuCl_3/NaIO_4$; aldehydes/ketones **8** may be synthesised directly from **5** by ozonolysis (for oxidation methods see for example the monograph by Hudlicky (Hudlicky) and references therein), but this process is not sufficiently selective and results in over-oxidation and the formation of other by-products. Preferred is the two step process of dihydroxylation (OsO_4, N-methylmorpholine-N-oxide (NMO),*t*BuOH/water) (VanRheenen *et al.*, 1976; Ray and Matteson, 1980) to **7** followed by oxidative cleavage ($Pb(OAc)_4$ in benzene or H_5IO_6 in THF).(Hudlicky, 1990) Examination of the products of the oxidation reactions led to the surprising discovery that cleavage with $Pb(OAc)_4$ resulted in isomerised product with the 4,5-substituents now trans. not cis as in the starting material. It was further

discovered that oxidation of the diol with H_5IO_6 in dry THF resulted in retention of the 4,5-cis configuration in the aldehyde product **8**. The cis aldehydes can also be isomerised to the trans by treatment with catalytic acid, e.g. HCl in $CHCl_3$.



8a 4,5-trans, inversion

7a 4,5-cis

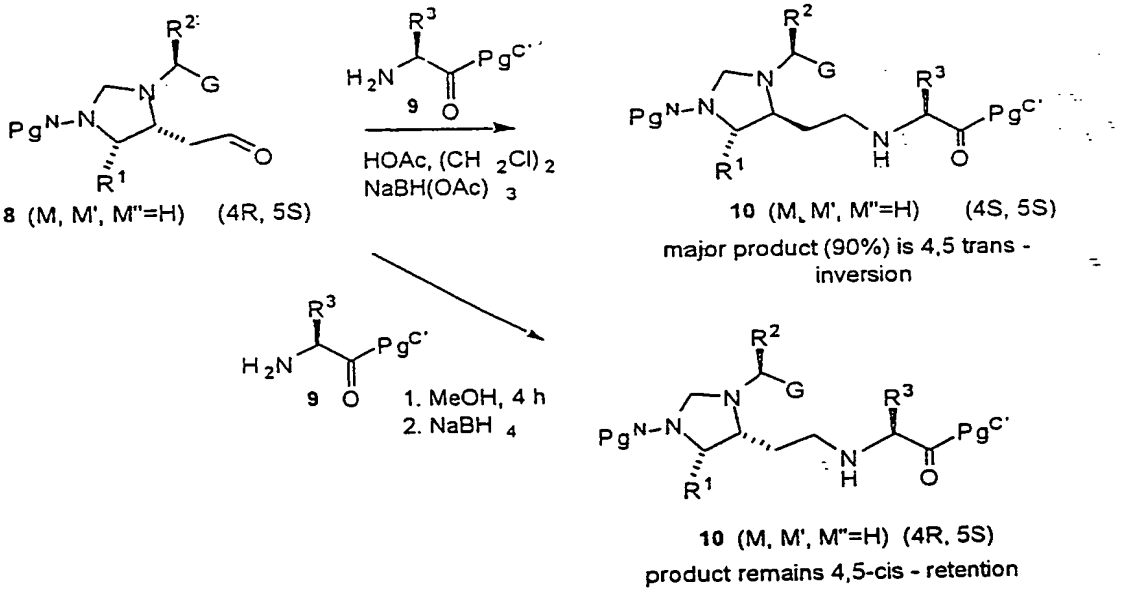
8a 4,5-cis. retention

These important discoveries now allow selective access to all of the eight possible diastereomers of the aldehydes **8** and the acids **6**, and therefore control of the majority of the chirality in all the mimetic systems described in the invention.

In relation to the oxidation of aldehydes **8** to acids **6**: many oxidation reagents may effect this conversion, e.g. pyridinium dichromate.(Hudlicky, 1990) Glycols **7** may also be oxidised directly to acids, e.g. by $RuCl_3/NaIO_4$. In relation to reduction of acids **6** to aldehydes **8**: carboxylic acids **6** can be converted to aldehydes by the same general methods used for the formation of protected □-amino aldehydes described above.(Jurczak and Golebiowski, 1989). The carboxylic acid can be selectively reduced to the alcohol in the presence of carboxylic esters by the use of borane (Brown and Krishnamurthy, 1979), then oxidised to the aldehyde as previously described.(Jurczak and Golebiowski, 1989)

In relation to **Scheme 2**: Aldehydes/ketones **8** undergo reductive amination with amino esters **9** by the methods previously described. The preferred method is $NaBH(OAc)_3$ in dichloroethane (room temperature). Surprisingly, it was discovered that the reductive amination of 4,5-cis imidazolidine aldehydes **8** resulted in the formation of the 4,5-

trans amines **10** (~9:1 trans:cis). This isomerisation reaction is rapid (much faster than that of aldehydes **8**) as the reductive amination reaction is complete in only a few minutes. It was further discovered that the isomerisation reaction could be prevented by the pre-formation of the imine between the aldehyde **8** and amine **9** (in MeOH, 2-4 h at room temperature) with rigorous exclusion of acid, followed by reduction with sodium borohydride to give the cis amine **10** from the cis aldehyde. This discovery allows the selective synthesis of either the 4,5-cis diastereomer or 4,5-trans (9:1 with cis) diastereomer of the amines **10** starting from the 4,5-cis aldehyde **8**.



It is important to appreciate that the methods described above allow the selective synthesis of all sixteen relative and absolute diastereomers of compounds **8** and **6**, and all thirty two diastereomers of compounds **10**. The ability to selectively synthesise these diastereomers is a significant advantage of the invention.

In relation to **Scheme 3**: Deprotection of **10** is by standard methods consistent with the overall protecting strategy, as previously discussed. Many coupling agents are suitable for effecting the cyclisation

of **11** to **12**, typical conditions: THF, BOP or HBTU or HATU, EtN(*i*-Pr)$_2$ (DIEA). The imidazolidine group is then deprotected (as previously described) by hydrogenation (MeOH, H_2-Pd/C) when Z = Me, and by hydrolysis (H^+, H_2O) for Z = H (other Z groups may be introduced by acylation or alkylation of the deprotected secondary amine).

In relation to **Scheme 4**: Deprotection and cyclisation of **6b** to **13**, **14** and **I(ii)**: - standard deprotection and coupling (cyclisation) methods are used. Other conversions are as previously described.

In relation to **Scheme 5**: As previously discussed, coupling reactions to relatively hindered (usually secondary) amines often require the use of specialised coupling conditions such as acid fluorides **15**, as described by Carpino *et al.* (Carpino *et al.*, 1990; Wenschuh *et al.*, 1994) Protecting groups $Pg^{N'}$ and $Pg^{C'}$ (in **16**) are typically benzyloxycarbonyl (Cbz) and benzyl ester, simultaneously deprotected by hydrogenation (0.1M HCl in EtOH, H_2-Pd/C), cyclised using the BOP coupling reagent in THF or DMF, followed by conversion (deprotection) of the imidazolidine group to N-Me by hydrogenation as previously described.

In relation to **Scheme 6**: Standard deprotection/ coupling conditions as previously described.

In relation to **Scheme 7**: Where R^4 is a □-branched amino acid side chain (such as in Valine) then the coupling of **6a** and **20** may require the use of HATU or other system suitable for a hindered coupling when bulky sidechain groups are present, as previously discussed. Conditions and protecting groups for the conversion of **21** to **19** are the same as for the conversion of **16** to **II(i)**, Scheme 5.

In relation to **Scheme 8**: Hydroboration of alkenes is well known in the art, see for example monographs by Brown (Brown, 1975; Pelter *et al.*, 1988) The resulting alkyl boranes can be oxidised to alcohols (using alkaline hydrogen peroxide, or in a preferred embodiment using trimethylamine oxide, or other amine oxide, to form the borate with subsequent liberation of the alcohol by transesterification) (Soderquist and Najafi, 1986). Alternatively, treatment of the borane with acid

dichromate or, in a preferred embodiment, with pyridinium chlorochromate (PCC) gives the aldehyde (Brown *et al.*, 1980; Brown *et al.*, 1986). The aldehydes so formed may be reductively aminated on to amines **9** by the methods previously described.

In relation to **Schemes 9-11**: Standard synthetic techniques, previously described.

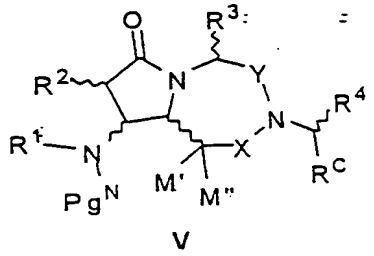
Methods for the synthesis of beta bulge (n=1, **III(i-iv)**) and higher loop mimetics (n>1), follow the corresponding methods for the synthesis of beta turn mimetics **II(i-iv)**. Appropriate protecting groups are chosen so that extra residues can be added to the system prior to cyclisation, as illustrated in Scheme 11 for the synthesis of a **III(i)** mimetic.

In relation to **Scheme 12**: Conversion of 1,2-diols **7** to epoxides **29** (dehydration) may be achieved with a number of reagents, for example triphenylphosphine and a dialkylazodicarboxylate (the Mitsunobu reagents) (Carlock and Mack, 1978; Robinson, Barry *et al.*, 1983) or TsCl/NaOH/$PhCH_2NEt_3^+$ Cl^-.(Szeja 1985). The epoxides **29** alkylate amines **9** on warming in ethanol or DMSO solution to give the amino alcohols **30**. The alcohol may then be oxidised to the ketone **32** by the use of TPAP (tetrapropylammonium perruthenate) with N-methylmorpholine-N-oxide in CH_2Cl_2/acetonitrile by the method of Griffith and Ley (Griffith and Ley ,1990). For **32** typically $Pg^{N'}$=Cbz and $Pg^{C'}$=O-benzyl, then by the use of catalytic hydrogenation conditions (EtOH, H_2-Pd/C) the protecting groups are both removed and intramolecular reductive amination of the free amine to the ketone occurs to give **33**. Coupling using the BOP reagent (or other suitable conditions) followed by deprotection of the imidazolidine group as previously described gives the bicyclic mimetic **IV(i)**. Alternative syntheses are possible with the use of mild oxidising reagents to convert the glycols to carbonyl compounds, followed by reductive amination (Frigerio and Sangostino, 1994).

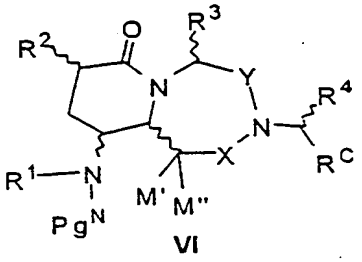
In relation to **Scheme 13**: 1,2 diols can be oxidised without carbon-carbon bond cleavage by the use of certain mild reagents e.g. IBX

(Frigerio and Sangostino, 1994). Conversion of **35c** to **36** proceeds by intramolecular reductive amination, or alternatively **35a** can be reductively aminated onto **2b**, as indicated. Reductive amination, coupling and deprotection details are as previously described.

The syntheses for the bicyclic □-turn mimetic systems **V** and **VI** are accomplished from the corresponding □-turn mimetic systems **I**, where the R^1 side chain group is derived from an aspartic acid (**V**) or glutamic acid (**VI**) derivative.



V



VI

	X	Y
V(i)	CH(M)	C(O)
V(ii)	C(O)	CH_2

	X	Y
VI(i)	CH(M)	C(O)
VI(ii)	C(O)	CH_2

The synthesis of mimetics **V** and **VI** thus proceeds as in Scheme 1, with the aldehyde component **1** (Scheme 1) being of the form **1d** or **1e** (Scheme 14), with the R and Pg groups as previously defined. The synthesis follows the synthesis of □-turn mimetic systems **I**, and is completed by the method illustrated in Scheme 15.

In relation to the preparation of alkylated aspartic and glutamic acid derivatives **1d** and **1e** the alkylated derivatives **39-42** can be prepared by a number of methods known in the art. Selected methods are summarised in Schemes 16 and 17. Rapoport and co-workers have developed methods for the selective alkylation of N-phenylfluorenyl protected aspartic and glutamic acid derivatives (Koskinen and Rapoport, 1989; Wolf and Rapoport, 1989). A review by Sardina and Rapoport, and references contained therein, describe several methods for the synthesis of alkylated aspartic and glutamic acid derivatives, incorporated herein by

reference (Sardina and Rapoport. 1996). Derivatives **39-42** are converted to aldehydes **1d** and **1e** by the methods previously described for for the preparation of aldehydes **1**.

The use of standard chemical techniques, in particular the Arndt-Eistert homologation reaction (Meier and Zeller, 1975) and reductions of carboxylic acids to aldehydes (Jurczak and Golebiowski, 1989), and also the synthesis of ketones -C(O)R from amides -C(O)N(OMe)Me (Nahm and Weinreb, 1981), to modify the aspartic and glutamic acid or their alkylated derivatives, or the use of similar derivatives of non-natural amino acids, such as homo-glutamic acid, enables the synthesis of the other compounds of the invention in which -Q^1Q^2- (in the general structure **X**) forms part of a cyclic system, defined as: -Q^1Q^2- = -$CH_2CH_2CH(R)C(O)$- (from sidechain alkylated homoglutamic acid); -$CH(R)CH_2$- (from aspartic acid by reduction of the □-carboxylate and reductive amination); -$CH_2CH(R)CH_2$- (from glutamic acid by reduction of the □-carboxylate and reductive amination); -$CH_2CH_2CH(R)CH_2$- (similarly from homoglutamic acid); -$CH_2CH(R)$- (from an aspartic acid sidechain ketone -$CH_2C(O)R$ by reductive amination); -$CH_2CH_2CH(R)$- (from a glutamic acid sidechain ketone -$CH_2CH_2C(O)R$ by reductive amination); -$CH(R)CH_2C(O)$- (post-alkylation sidechain homologated aspartic acid); -$CH_2CH(R)CH_2C(O)$- (post-alkylation sidechain homologated glutamic acid); -$CH(R)CH_2CH_2$- or -$CH_2CH(R)CH_2CH_2$- (from reductive amination of reduced post-alkylation sidechain homologated aspartic acid or glutamic acid derivatives).

In relation to **Scheme 18**: An alternative procedure for the synthesis of intermediate compounds **10** (or equivalent) can be used in the case where R^1 is hydrogen and M, M' and M'' are also hydrogen, as described in Scheme 18. Compound **49** is available commercially with certain N-protecting groups or can be made by coupling N-protected glycine with N,O-dimethylhydroxylamine. Reaction with vinylmagnesium bromide in analogy to the general procedure of Rapoport and co-workers

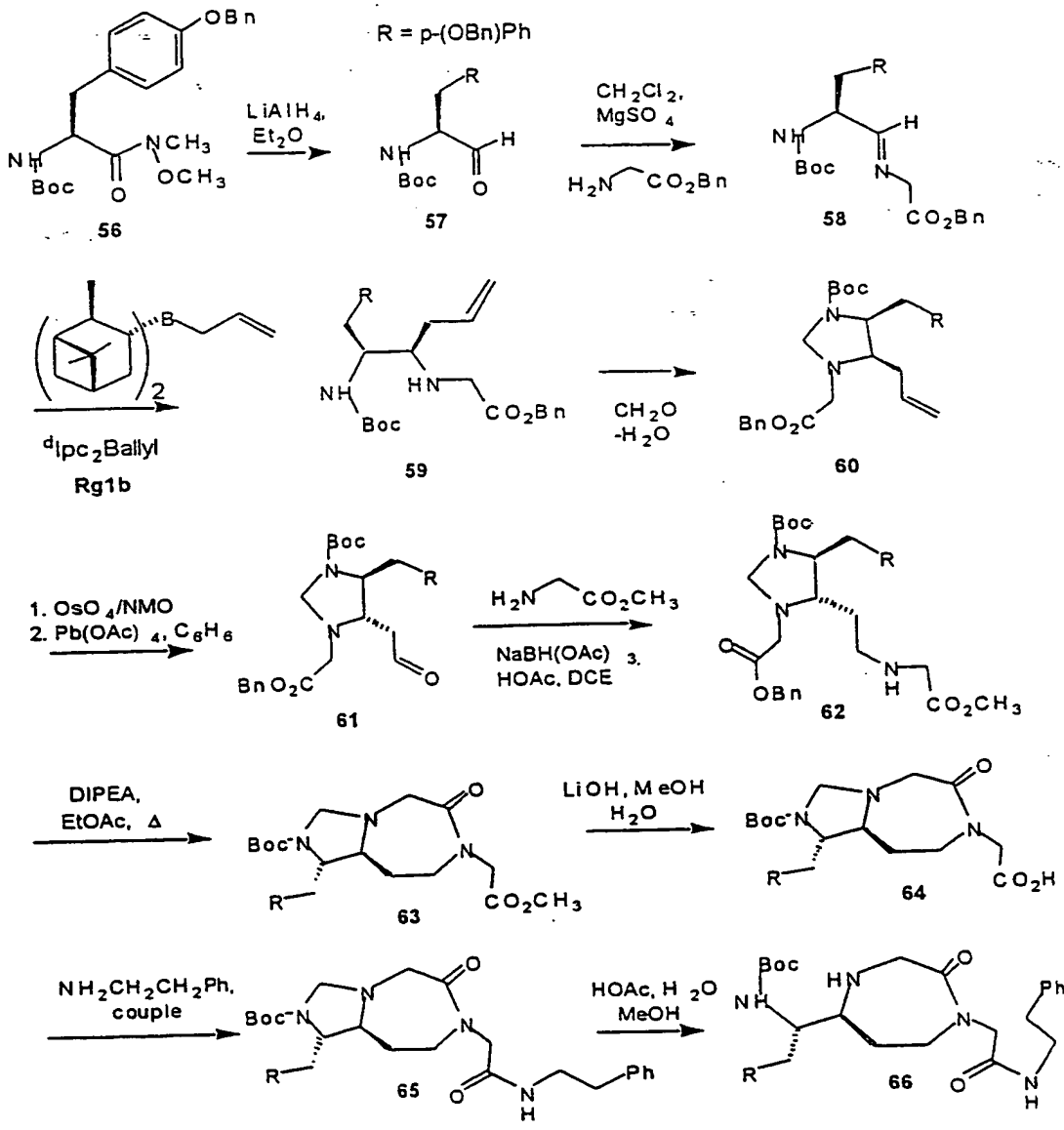
(Cupps *et al.*, 1985; Boutin and Rapoport, 1986) results in formation of the □,□-unsaturated ketone **50**. Conjugate addition of an amino acid ester **9** (0_C, THF) results in the formation of aminoketones **51** which can be N-protected by standard procedures to form ketones **52** before reductive amination of an amino acid ester **9** under the conditions described by Abdel-Magid *et al.* (Abdel-Magid *et al.*, 1996) ($NaBH(OAc)_3$, dichloroethane) to form **54**. Deprotection to **55** and coupling gives the □-turn mimetics **I(i)a** (where R^1=H) as indicated. Alternatively the aminoketones **51** can be acylated with an amino acid fluoride **15** to give compounds **53** which can be deprotected and cyclised (by reductive amination) by hydrogenation in mild acid conditions (H_2/Pd-C, 0.1M HCl in EtOH). The reductive amination-cyclisation is diastereoselective, only one diastereomer of the mimetics **I(i)a** were formed from **53**, with the configuration at the new stereocentre controlled by the R^2 stereocentre. The (S) configuration at R^2 gives (S) at the new centre. In contrast, the reductive amination to form amines **54** proceeds with lower stereoselectivity (~3:1) with the major diastereomer having the (R) configuration when R^2 is (S). These discoveries provide further opportunity for stereocontrol in the synthesis of the turm mimetics. Deprotection of compounds **54** and reaction with formalin in THF is an alternative method for synthesis of compounds **10** (R^1=H), as described in Scheme 18.

EXAMPLE SYNTHESES

Example (A). *Synthesis of a □-turn mimetic I(i) by the general procedure*

A mimetic for the sequence HTyr-Gly-Gly-Phe, which is found in the enkephalins, was synthesised with a □-turn mimetic based on the Tyr-Gly-Gly tripeptide. Similar mimetics have shown activity at opiate receptors (Huffman, Callahan *et al.*,1988; Huffman *et al.*, 1989).

The synthesis is summarised in the following scheme:-



Preparation of **56**:

The amide **56** was synthesised from commercially avaliable Boc-Tyrosine(OBn)OH by coupling with N,O-dimethylhydroxylamine hydrochloride, 1 equivalent, in DMF/CH_2Cl_2 (1:5) using HBTU reagent (1 eq.) and DIEA (2 eq.) at room temperature. The CH_2Cl_2 was evaporated *in vacuo* and the residue partitioned between diethyl ether and aq. $NaHCO_3$. The aqueous layer was separated and the ether layer washed in turn with 1M HCl (x2), aq. $NaHCO_3$, brine, and then dried over $MgSO_4$. Filtration and removal of the solvent *in vacuo* left the product amide **56** as a white crystalline solid in >90% yield. Further purification was carried out by silica gel chromatography eluting with ethyl acetate in petroleum ether, or by recrystallisation from ether. **^{1}H NMR** (300 MHz, $CDCl_3$): □ 7.46-7.28, 5H, m, OBn; 7.08, 2H, d, J=8.5 Hz, Tyr Ar; 6.90, 2H, d, J=8.5 Hz, Tyr Ar; 5.15, bd, J=8 Hz, NH; 5.04, 2H, s,)OCH_2Ph; 4.91, 1H, bm, Phe□; 3.65, 3H, s, OCH_3; 3.16, 3H, bs, NCH_3; 3.00, 1H, dd, J=6, 13.5 Hz, Phe□; 2.83, 1H, dd, J=7, 13.5 Hz, Phe□; 1.40, 9H, s, Boc. **^{13}C NMR** (75 MHz, $CDCl_3$): □ 172.3; 157.6, Tyr Ar-O; 155.1, carbamate; 137.0, ipso; 130.4; 128.8; 128.5; 127.8; 127.4; 114.7; 79.5, tBoc; 69.89, OCH_2Ph; 61.43, Tyr□; 51.55, OCH_3; 37.89, NCH_3; 32.00, Tyr□; 28.26, Boc.

Preparation of **57**:

The aldehyde **57** was prepared by the method of Fehrentz and Castro (Fehrentz and Castro, 1983) as follows: to a stirred solution of 4.2 g of amide **56** in 100 mls of anhydrous diethylether cooled to 0°C was added 0.51 g lithium aluminium hydride. After 10 minutes a solution of 1.5g $NaHSO_4$ in 30 mls of water was added. The reaction mixture was diluted with more ether and washed with 1M HCl, saturated aqueous sodium bicarbonate and brine and dried over magnesium sulphate. The volatiles were removed under reduced pressure to give a waxy solid which was recrystallised from cold ether/hexane to give 2.6 g (72%) of **57** as a white solid. **^{1}H NMR** (300 MHz, $CDCl_3$): □ 9.62, 1H, s, aldehyde; 7.50-7.25, 5H, m, Ar(OBn); 7.10, d, J=8 Hz, Ar(Tyr); 6.93, 2H, d, J=8 Hz,

Ar(Tyr); 5.10, 1H, b, NH; 5.05, 2H, s, OCH_2Ph; 4.39, 1H, q, J=7 Hz; Tyr□; 3.06, 2H, d(ABX), J=7 Hz, Tyr□; 1.44, 9H, s, Boc. **^{13}C NMR** (75 MHz, $CDCl_3$): □ 199.6; 157.8, TyrOAr; 155.3, carbamate; 136.9, ipso; 130.3; 128.5, 127.9, 127.4: ArCH; 115.0, ArCHTyr; 80.08, tBoc; 69.69, OCH_2Ph; 60.82, Tyr□; 34.51, Tyr□; 28.22, Boc.

Preparation of **58**:

The imine **58** was formed by the reaction of the aldehyde **57** (1.4 g) with one equivalent of glycine benzyl ester in 10ml CH_2Cl_2 (stir at room temperature 1 h) the water formed was removed with magnesium sulphate which was then removed by filtration.

^{1}H NMR (300 MHz, $CDCl_3$): □ 7.68, 1H, s, imine; 7.49-7.30, 10H, Ar; 7.15, 2H, d, J=8 Hz, TyrAr; 6.92, 2H, d, J=8 Hz, TyrAr; 5.67, 1H, bd, J=6 Hz, NH; 5.20, 2H, s, OCH_2Ph; 5.05, 2H, s, OCH_2Ph; 4.51, 1H, bm, Tyr□; (4.26, 4.22), 2H, AB, J=15.5 Hz, Gly□; 3.15, 1H, bdd, J=5.0, 13.5 Hz, Tyrb; 2.93, 1H, dd, J=8.0, 13.5 Hz, Tyrb; 1.48, 9H, s, Boc. **^{13}C NMR** (75 MHz, $CDCl_3$): □ 169.3; 167.4, CH imine; 157.5; 155.1; 136.9, 135.3: 2x ipso; 130.4, CHAr; 128.8, Tyr ipso; 128.44, 128.39, 128.26, 128.19, 127.76, 127.29, 114.65: ArCH; 79.22, tBoc; 69.81, TyrOCH_2Ph; 66.60, GlyOCH_2Ph; 60.48, Tyr□; 54.73, Gly□; 37.97, Tyr□; 28.23, Boc.

Preparation of **59**:

A 0.5 molar solution of allyl borane reagent ^{d}Ipc$_2$Ballyl (**Rg1b**) was prepared by the addition of allylmagnesium bromide to one equivalent of (+)DIP-Cl in anhydrous diethyl ether under dry nitrogen. Brown and Jadhav, 1983). The solution of imine **58** in CH_2Cl_2 was stirred and cooled to -78°C under dry nitrogen and one equivalent of the previously prepared ^{d}Ipc$_2$Ballyl solution added. The mixture was allowed to warm gradually to room temperature (overnight). The volatiles were removed under reduced pressure and the residue dissolved in THF and 1 ml of glacial acetic acid added. The mixture was refluxed overnight and then the volatiles removed under reduced pressure. The crude product was dissolved in CH_2Cl_2 / petroleum ether and the precipitate filtered off.

The residual oil was chromatographed on flash silica eluting with ethyl acetate / petroleum ether to give 1.3 g (60% yield based on **57**) of **59**. TLC 1:2 EtOAc:light pet. Rf=0.40. **^{1}H NMR** (300 MHz, $CDCl_3$): □ 7.48-7.30; 10H, Ar; 7.13, 2H, d, J=8.5 Hz, TyrAr; 6.91, 2H, d, J=8.5 Hz, TyrAr; 5.84, 1H, m, vinyl CH; 5.17, 2H, s, TyrOCH_2Ph; 5.16, 2H, m, vinyl CH_2; 5.05, 2H, s, GlyOCH_2Ph; 4.90, 1H, bd, J=8.5 Hz, NHBoc; 3.95, 1H, bm, Tyr□; 3.54, 2H, s, Gly□; 3.82, 1H, dd, J=4.5, 14.4 Hz, Tyr□; 2.73, 3H, be: NH(amine), Tyr□, CH(homoallyl); 2.28, 2H, m, allyl; 1.35, 9H, Boc. **^{13}C NMR** (75 MHz, $CDCl_3$): □ 172.1; 157.3; 155.6; 137.1, 135.4: ipso; 134.9, CHvinyl; 130.6, ipsoTyr; 130.0, 128.5, 128.4, 128.3, 127.8, 127.3: ArCH; 117.8, CH_2vinyl; 114.7, TyrArCH; 79.05, tBoc; 69.90, TyrOCH_2Ph; 66.51, GlyOCH_2Ph; 59.38, Tyr□; 53.46, CH; 49.28, Gly□; 35.44: coincident allyl carbon and Tyr□; 28.20, Boc. Mass Spectrum (ISMS) m/z 545.1 (MH^+), calculated for $C_{32}H_{45}N_3O_5$: 544.

Preparation of **60**:

The amine **59** (930 mg, 1.7 mmol) was dissolved in ethyl acetate (15 mL) and 37% aq. formaldehyde solution added (1 mL). The solution was stirred vigorously at room temperature for 1 h (or until the reaction was complete) and then diluted with ether (100 mL) and washed in turn with aq. $NaHCO_3$, water (x3), brine and then dried ($MgSO_4$). Removal of solvent *in vacuo* left an approximately quantitative yield (950 mg) of the crude product **60** which was used in the next reaction or further purified by flash chromatography eluting with 10-15% ethyl acetate in light petroleum. TLC 33%EtOAc:light pet. Rf=0.56. The NMR spectra were quite broad in $CDCl_3$, amide rotamers were present in the approximate ratio 2:1. **^{1}H NMR** (300 MHz, $CDCl_3$): □ 7.50-7.27, 10H, m's, Ar; 7.09, 2H, m, Ar; 6.90, 2H, d, J=8.5 Hz, Ar; 5.64, 1H, bm, vinyl CH; 5.19, 2H, s, OCH_2Bn; ~5.1, 2H, m, vinyl CH_2; 5.05, 2H, s, OCH_2Bn; 4.59, 1H, bm, ring NCH_2N(a); 4.17, 1H, bm, ring NCH_2N(b); 4.06, 1H, bm, Tyr□; 3.70, 1H, d, J=17 Hz, Gly□(a); 3.42, 1H, bd, J=17 Hz, Gly□(b); 3.16, 1H, bm, TyrC'H(ring); 2.84, 2H, bm, Tyr□; 2.31, 2H, m, allylCH_2; 1.38, ~3H, bs, Boc minor rotamer; 1.19, ~6H, s, Boc major rotamer. **^{13}C NMR** (75 MHz,

$CDCl_3$): □□□(peaks due to the carbamate rotamers are placed in parentheses, major rotamer first) 169.8 (ester); 157.2 (tyrosine O-ipso); (153.1, 152.8) carbamate; 137.2 (ipso); 135.4 (ipso); 134.2 (CH vinyl); 131.3 (ipso); 130.5, 128.5, 128.4, 128.3, 127.8, 127.4, 127.3, 126.9: ArCH; 117.5 (vinyl CH_2); 114.7 (2xTyrArCH); 79.52 (Boc tertiary); 69.93 (CH_2); 66.95 (CH_2); 66.46 (CH_2); 64.27 (CH); (59.65, 58.76) (CH); 51.60 (CH_2); 34.34 (CH_2); (32.20, 31.93) (CH_2); (27.93, 28.25) (Boc 3xCH_3). Mass Spectrum (ISMS) m/z 557.1 (MH^+), calculated for $C_{34}H_{40}N_2O_5$: 556 fragments (OR 60): 501.1, (-tBu).

Preparation of **61**:

To 220 mg of **60** was added 60 mg of N-methylmorpholine-N-oxide (NMO), 40 mg of a 2.5% (by weight) solution of osmium tetroxide in *t*-butanol, 4 mls of *t*-butanol and 0.5 mls water. The mixture was stirred at room temperature until the reaction was complete (about 24 hours). 3 mls of 10% $NaHSO_3$ was added, the solution stirred for 10 minutes, then neutralised with sodium bicarbonate, diluted with brine and extracted three times with ethyl acetate. The combined extracts were washed with brine and dried over magnesium sulfate. Removal of volatiles under reduced pressure gave the crude diol in good yield as an oil which could be used in the next reaction or purified if required by chromatography on silica gel eluting with ethyl acetate. Mass Spectrum (ISMS) m/z 591.3 (MH^+), calculated for $C_{34}H_{42}N_2O_7$: 590.

Oxidation of diol using $Pb(OAc)_4$: The diol (100 mg, 0.17 mmol) was dissolved in dry benzene (4 mL) and $Pb(OAc)_4$ (85 mg, moistened with acetic acid) was added. After 10 min stirring at room temperature the reaction was filtered, the solvent removed *in vacuo* and the residue purified by flash chromatography eluting with 25%EtOAc in light petroleum. Yield of the aldehyde **61** was 32% (30 mg). (No efforts to optimise the yield were made. Yield might be improved, for example, by partitioning the crude reaction mixture between aq.base and EtOAc to ensure none of the amine product was lost on filtration of the insoluble salts.) TLC 50%EtOAc in light pet. Rf=0.51. NMR analysis (NOESY

experiment) indicated the 4,5-trans ring conformation (i.e. the 4(S) isomer). **^{1}H NMR** (300 MHz, $CDCl_3$): □ 9.52, 1H, t, J=1.5 Hz, aldehyde; 7.50-7.25, 10H, m, ArH; 6.92, 2H, d, J=9 Hz, TyrAr; 5.15, 2H, s, OCH_2Ph; 5.05, 2H, s, OCH_2Ph; 4.65, 1H, bm, ringCH_2(i); 3.88, 1H, bm, Tyr□; 3.80, 1H, bm, ringCH_2(ii); 3.45, 1H, d, J=16 Hz, Gly□; 3.44, 1H, m, ringCH(□aldehyde); 3.28, bd, J=16 Hz, Gly□; 3.17, 1H, bm, Tyr□; 2.80, 1H, dd, J=9.0, 13.5 Hz, Tyr□; 2.51, 1H, J=6, 17 Hz, □aldehyde; 2.28, 1H, dd, J=17, 4.5 Hz, □aldehyde; 1.50, 9H, Boc. **^{13}C NMR** (75 MHz, $CDCl_3$), (rotamers): □ 200.5; 169.9; 157.5; 153.1; 136.9; 135.3; 130.5, 129.6, 128.6, 128.5, 128.4, 127.6, 127.4, 115.0: Ar; 80.21, tBoc; 69.92, OCH_2Ph; (67.08, 66.86) br, CH_2; 66.58, OCH_2Ph; (62.93, 62.56) br, CH; (61.35, 60.72) br, CH; 52.14, CH_2; 46.36, CH_2; (38.5, 37.27) br, CH_2; 28.38, Boc. Mass Spectrum (ISMS) m/z 559.1 (MH^+), calculated for $C_{33}H_{38}N_2O_6$: 558.

Preparation of **62** and **63**:

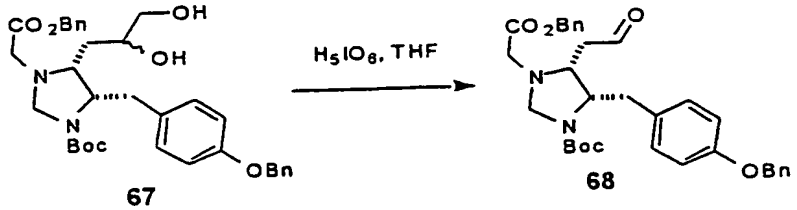
The aldehyde **61** (30 mg, 50□mol) was dissolved in 1.2-dichloroethane (5 mL) and glycine methyl ester hydrochloride (50 mg) and $NaBH(OAc)_3$ (50 mg) added. The reaction was stirred at room temperature and was complete in a few minutes (<15 min). The reaction was diluted with ethyl acetate, and washed in turn with aq.$NaHCO_3$, water, brine and then dried ($MgSO_4$). Evaporation of the solvent left the crude product **62** as a clear oil: TLC 1:1 EtOAc:light pet. Rf=0.17. Mass Spectrum (ISMS) m/z 632.3 ($M+H^+$), calculated for $C_{32}H_{45}N_3O_5$: 631 Analysis of the product or the reaction mixture after overnight standing revealed the formation of a new product with a mass spectrum corresponding to the target cyclised material **63** (MH^+=524Da). Thus the amine product **62** was not generally isolated but converted directly to **63**. The spontaneous cyclisation was accelerated by the addition of base (*i*-Pr_2NEt). After removal of solvent by evaporation under reduced pressure and the product was purified by flash chromatography eluting with 10-20% EtOAc in light pet. TLC: 1:1 EtOAc:light pet. Rf=0.51. **^{1}H NMR** (300 MHz, CD_3CN): □ 7.47-7.29, 5H, m, ArH; 7.12, 2H, m, Tyr; 6.92,

2H, m, Tyr; 5.07, 2H, s, $OC\underline{H}_2Ph$; 4.35, 1H, d, J=5.4 Hz; ABq, □a=4.05, □b=4.02, J_{AB}=17.4 Hz; 3.70-3.52, 6H, overlapped signals (includes: 3.65, 3H, s; 3.58, 1H, dd, J=11.2, 15.2 Hz); 3.49-3.32, 2H, br m's; 3.15, 1H, br dd, J=5.5, 15.5 Hz; 2.99, 1H, br dd, J=13.4, 14.9 Hz; 2.80, 1H, vbr m; 2.68, 1H, vbr m; 1.64, 1H, m; 1.46, 10H, s + m, Boc resonance obscures multiplet. **^{13}C NMR** (75 MHz, CD_3CN), rotamers, in approximate ratio 3:2, split some peaks and are recorded in parentheses: □ 173.3; 171.5; 158.8; 155.0, br; 138.9; 132.0; 129.9; 129.2; 129.0; 116.1; 80.84; 71.01; (70.87, 69.99); (68.12, 67.45); (65.47, 64.89); 55.76; 52.93; 51.45; 49.95; (39.00, 37.53); 31.87; 28.97 (Boc). Mass Spectrum (ISMS) m/z 524.3 ($M+H^+$), calculated for $C_{29}H_{37}N_3O_6$: 523.

Preparation of compounds **64** to **66**:

The product **63** was hydrolysed with $LiOH/H_2O$/MeOH to the acid **64** (mass spectrum MH^+=510) and then coupled (DMF/CH_2Cl_2/HBTU/DIEA) with phenethylamine using standard procedures and work-up to give **65**. The imidazolidine ring of **65** was deprotected with a solution of acetic acid-methanol-water (~1:1:1, stirred as a very dilute solution for several days then lyophilised) to give crude **66** as a white amorphous solid. Mass Spectrum (ISMS) m/z 601 ($M+H^+$), calculated for $C_{35}H_{44}N_4O_5$: 600.

Example (B). *Synthesis of a (4,5)-cis imidazolidine aldehyde by oxidation of a diol.*

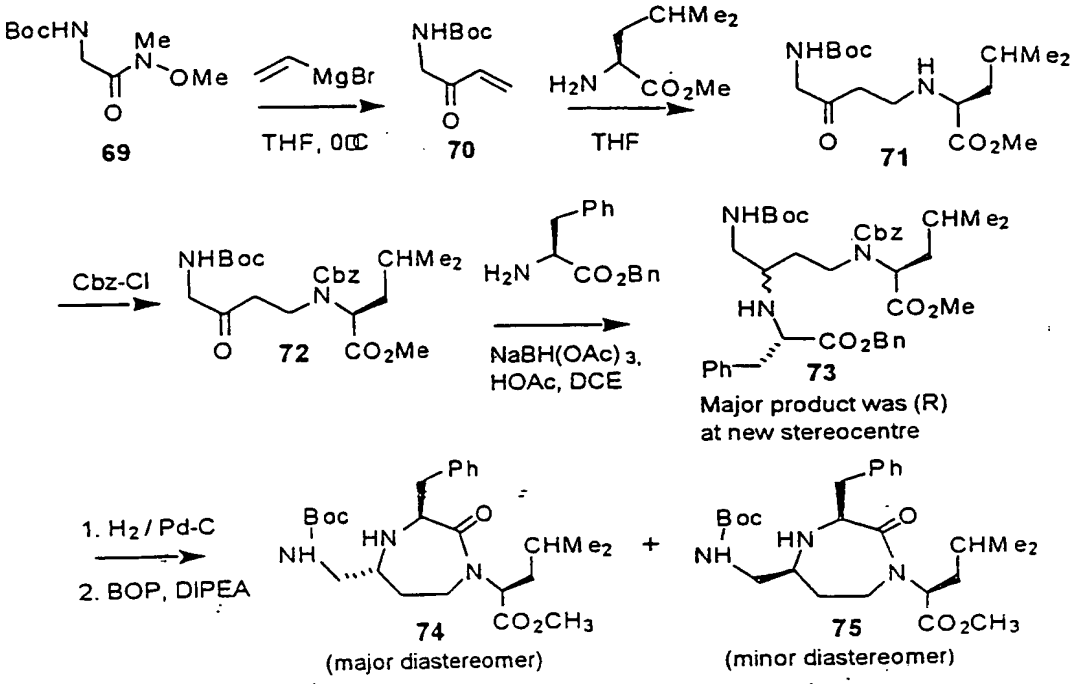


67 68

For the preparation of the 4,5-cis aldehyde **68** (in this case the 4(R) isomer) the diol **67** prepared from alkene **60** (as described above) (1mmol) was dissolved in THF (10 mL) and H_5IO_6 (1 mmol)

dissolved in THF (~20 mL) was added and the reaction stirred at room temperature. A precipitate of iodic acid rapidly formed and the reaction was complete in <5 min. The THF solution was diluted with ether and washed in turn with 10% aq.Na_2CO_3, water, brine and then dried ($MgSO_4$). The product aldehyde **68** was formed in good yield and purity. Contact with acid should be minimised to prevent isomerisation to the trans aldehyde and/or decomposition, for example avoid chloroform as an NMR solvent unless recently made acid free. Yield was 60-80%. TLC: 50%EtOAc in light pet. Rf=~0.5. **^{1}H NMR** (300 MHz, CD_3CN): □ (peaks moderately broad; the Boc rotamers were not resolved although the Boc peak was asymmetric and very broad) 9.48, 1H, bm, aldehyde; 7.5-7.3, 10H, m, 2xBn; 7.09, 2H, bd, J=7.5 Hz, Tyr Ar; 6.88, d, 8.2 Hz, Tyr Ar; 5.13, s, 2H, OCH_2Ph; 5.05, s, 2H, OCH_2Ph; 4.38, 1H, d, 6.0 Hz, NCH_2N(a); 4.22, 1H, m, Tyr□; 4.02, 1H, br, NCH_2N(b); 3.56, 1H, bd, J=17.2 Hz, Gly□(a); 3.48, 1H, m, TyrC'H; 3.29, 1H, bd, J=17.2 Hz, Gly□(b); 2.57-2.88, 4H, e, Tyr□ CH_2 and □-aldehyde CH_2; 2.22, s, H_2O; 1.48-1.08 (1.20 peak), 9H, vbr, Boc 3xCH_3. **^{13}C NMR** (75 MHz, CD_3CN): □ 201.9; 171.4; 158.7; 154.3; 139.0; 137.6; 132.6; 131.9, 129.92, 129.85, 129.6, 129.2, 128.9, 116.0: ArCH; 80.41 (Boc tert.); 70.99 (CH_2); 67.62 (br, CH_2); 67.44 (br, CH_2); 60.29 (2xCH, co-incident peaks determined by comparative intensity); 52.99 (br, CH_2); 43.58 (br, CH_2); 35.94 (br, CH_2); 28.78 (br, Boc 3xCH_3).

Example (C). *Synthesis of □-turn mimetics I(i) for the Gly-Phe-Leu sequence by the short method (which can be used when R^1 = hydrogen)*



Preparation of **69**:

Boc-glycine was coupled with N,O-dimethyl hydroxylamine hydrochloride, 1 equivalent, in DMF/CH_2Cl_2 (1:5) using HBTU reagent (1 eq.) and DIEA (2 eq.) at room temperature. The CH_2Cl_2 was evaporated *in vacuo* and the residue partitioned between diethyl ether and aq. $NaHCO_3$. The aqueous layer was separated and the ether layer washed in turn with 1M HCl (x2), aq. $NaHCO_3$, brine, and then dried over $MgSO_4$. Filtration and removal of the solvent *in vacuo* left the product amide **69** as a viscous oil that slowly crystallised to a waxy solid and was further purified by chromatography on silica gel. Yield was >90%. **^{1}H NMR** (300 MHz, $CDCl_3$): □ 5.3, 1H, bs, NH; 4.09, 2H, bd, □H_2; 3.72, 3H, s, OCH_3; 3.20, 3H, s, NCH_3; 1.46, 9H, s, Boc. **^{13}C NMR** (75 MHz, $CDCl_3$): □ 79.6; 61.4; 41.7; 32.4; 28.3.

Preparation of **70**:

A solution of 11.6 g (53 mmol) of Boc-glycine N,O-dimethylhydroxylamide in dry THF (70 mL) under nitrogen in a 250 mL round bottom flask was stirred and cooled in an ice bath. To this was added vinyl magnesium bromide in THF (~120 mmol of a 1M solution) by

syringe over 10 minutes. The solution was stirred for 2 h and then quenched by pouring into a mixture of crushed ice and 1M HCl which was then extracted with CH_2Cl_2 (x2). The organic extracts were washed with water/brine (x2), aq. $NaHCO_3$ and water/brine followed by drying over $MgSO_4$. Evaporation of the solvent left 9.6 g of a mobile oil (98% crude) which by NMR was ~95% the ketone product **70**. This material was used without further purification in the conjugate addition step. **^{1}H NMR** (300 MHz, $CDCl_3$): □ 6.37, 2H, m (ABX, J_{ab}=2.5 Hz, $J_{ax/bx}$=9.0, 17.5 Hz), vinyl CH_2; 5.95, 1H, dd, J=2.5, 9.0 Hz, vinyl CH; 5.37, 1H, bs, NH; 4.26, 2H, d, J=4.6 Hz, glycyl □H_2; 1.46, 9H, s, Boc. **^{13}C NMR** (75 MHz, $CDCl_3$): □ 194.9 ketone; 155.8 carbamate; 133.6 vinyl; 129.6 vinyl; 79.8 tBoc; 48.32 Gly□; 28.28 Boc.

Preparation of **71**:

To a solution of 3.0 g (~15 mmol) of crude **70** in THF (40 mL) was added 3.4 g of leucine methyl ester hydrochloride (~1.2 eq) and 2.4 g (1.2 eq) of diisopropylethylamine. After 2 h the reaction was diluted with ether (200 mL) and extracted with cold 1M HCl (3x50 mL) (discard this ether layer). The aq. extracts were immediately neutralised with solid $NaHCO_3$ and this solution was then back extracted with ether, and the ether washed with water (x3) and finally brine and dried over $MgSO_4$. Evaporation of the solvent left ~5.3 g of product **71** as an oil with very good purity, contaminated with a small amount of leucine methyl ester. Flash chromatography to separate the product was not very successful as the amine and amino ketone tended to co-elute. TLC EA/LP Rf=0.35. **^{1}H NMR** (300 MHz, $CDCl_3$): □ 5.36, 1H, bm, NHBoc; 4.03, 2H, d, J=5 Hz, Gly□; 3.72, 3H, s, OCH_3; 3.26, 1H, t, J=7.5 Hz, Leu□; 2.93, 1H, dt, J=12, 6 Hz; 2.72, 1H, dt, J=12, 6 Hz; 2.50, 2H, m; 2.0, 1H, bs, NH; 1.69, 1H, m, Leu□; 1.45, 11H, m, Boc(9H) and Leu□(2H); 0.90, 6H, m, Leu□. **^{13}C NMR** (75 MHz, $CDCl_3$): □ 205.1; 176.1; 155.5; 79.8 tBoc; 60.04; 51.64; 50.53; 42.63; 42.57; 40.55; 28.26 Boc; 24.81; 22.63; 22.17. Mass Spectrum (ISMS) m/z 331.4 ($M+H^+$), calculated for $C_{16}H_{30}N_2O_5$: 330; fragments (OR 60): 275.2 (-tBu).

Preparation of **72**:

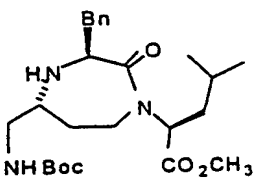
The amine **71** was protected as the benzyl carbamate by standard procedures as follows: the crude amine product **71** (1.68 g, ~5 mmol) was dissolved in ethyl acetate (30 mL) to which was added a solution of $KHCO_3$ (1.2 g) in water (15 mL). This mixture was vigorously stirred and cooled in an ice bath and to it was added benzyl chloroformate (780 uL of a 95% solution, 5.2 mmol) dropwise over 5 min. The reaction was stirred for a further 15 min then allowed to warm to room temperature with stirring for an additional 2 h. After this time the mixture was diluted with ether (100 mL), the aqueous layer seperated, and the organic layer washed with 1M HCl, aq. $NaHCO_3$, brine and then dried over $MgSO_4$. Evaporation of the solvent left ~2.6 g crude oil which was purified by flash chromatography eluting with 25%EtOAc in light pet; combination of the main fractions gave a yield of 86% (2.02 g) of **72**. TLC EA:2LP Rf=0.56.. NMR signals split due to amide rotamers (~1:1) are placed in parentheses where possible. **^{1}H NMR** (300 MHz, $CDCl_3$): □ 7.40-7.23, 5H, Ar; 5.28-5.02, 3H, m's, CH_2Ph + NH; (4.64, m, 4.43, m) 1H; (3.98, bs, 3.88, bs) 2H; 3.72-3.51, 4H, includes (3.67, s, 3.55, s) OCH_3 + 1H; 3.45, 1H, m; 2.78, 2H, m; 1.75, 2H, m; 1.53, 1H, m; 1.43, 9H, s, Boc; 0.91, 6H, m, Leu□ CH_3x2. **^{13}C NMR** (75 MHz, $CDCl_3$): □ (204.9, 204.5) ketone; (172.5, 172.3) ester; (156.1, 155.8) carbamate; 155.6, carbamate; (136.2, 136.0) ipso; 128.5, 128.2, 128.1, 128.0: ArCH; 79.80, tBoc; 67.48; (58.50, 58.32); 52.12; 50.30; (41.37, 39.87, 39.78, 38.87, 38.60, 37.98) 3C; 28.23, Boc; (24.83, 24.67); 23.09; (21.46, 21.39). Mass Spectrum (ISMS) m/z 465.3 (MH^+), calculated for $C_{24}H_{36}N_2O_7$: 464; fragments (OR 70): 409.2, (-tBu); 365.2, (-Boc).

Preparation of amines **73**:

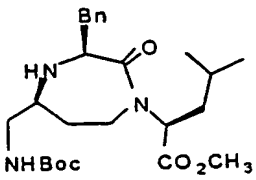
To a solution of **72** (700 mg, 1.5 mmol) in 15 mL of 1,2-dichloroethane was added phenylalanine benzyl ester p-toluene sulfonate (900 mg, 2.1 mmol) and sodium triacetoxy borohydride (850 mg, 4.0 mmol). The mixture was stirred at room temperature for 24 h and then the solvent removed under vacuum and the residue partitioned between ethyl

acetate and aq. $NaHCO_3$, the aqueous layer separated, and the organic layer washed with water then brine and then dried over $MgSO_4$. Evaporation of the solvent left 1.2 g crude oil which was purified by flash chromatography eluting with 25-40% EtOAc in light petroleum ether to give a yield of 76% (800 mg) of the product (a clear oil). The product diastereomers **73** were not seperable under these chromatography conditions. TLC 40%EA in LP Rf=0.48. **^{1}H NMR** (300 MHz, CD_3CN): □ (not very informative due to the presence of rotamers/diastereomers) 7.45-7.05 aromatic protons; (5.46 m, 5.31 m)~1/2H; 5.15-5.00, ~4H, m, OCH_2Ph; 4.95, ~1/4H, m; (4.51, m, 4.37, m): 1H; 3.85-3.10, ~5H, e (including 3.63, s, 3.58, s: 3H, OCH_3); 3.10-2.70, 5H, e; 2.45 broad water peak; 1.80-1.45, 5H, m's; 1.40, 9H, s, Boc; 0.90, 6H, bs, Leu□. **^{13}C NMR** (75 MHz, CD_3CN): □ (signals are grouped in parentheses where they can be reasonably assigned to equivalent carbons in the different diastereomers/rotamers) (175.6, 175.4(br)); 173.6; 157.4, 157.2 (br); (139.0, 139.2, 138.5, 138.3, 137.3) 3x ipso; 130.8, 130.7 129.9 129.71, 129.66, 129.3, 129.0, 128.0: Ar CH; (79.87, 79.62) Boc tertiary; 68.22 (CH_2, OBn); 67.75 (CH_2, OBn); (61.67, 61.55) (CH); 59:39 (CH); (56.51, 55.82, 55.61) (CH); 53.11 (OCH_3); (45.56, 45.16, 44.73, 44.61, 44.43, 44.24, 43.42, 43.04) (2xCH_2); (40.77, 40.15, 40.03, 39.42, 39.27) (2xCH_2); (39.66, 32.60, 32.45, 31.44) (CH_2); 29.04 (CH_3 Boc); 29.93 (CH); 23.88 (CH_2); 22.36 (CH_2). Mass Spectrum (ISMS) m/z 704.4 ($M+H^+$), calculated for $C_{40}H_{53}N_3O_8$: 703.

Preparation of **74** and **75**:



74 (R) - major product



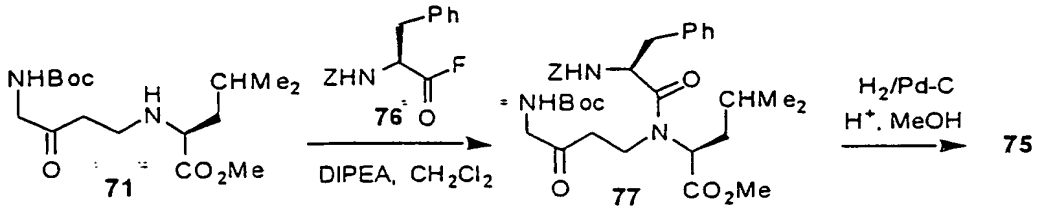
75 (S) - minor product

The mixture of epimeric amines **73** (260 mg, 0.4 mmol) was dissolved in methanol (20 mL) and 10% palladium on carbon added (100

mg). The solution was hydrogenated (40 psi H_2) at room temperature for 3 h to give the deprotected amino acid (MH^+=480Da). After filtration, the solvent was removed and the residue (170 mg) was dissolved in DMF (5 mL) and diluted with CH_2Cl_2 (50 mL). To this solution was added HBTU (180 mg, 0.48 mmol) and DIEA (150 mg, 1.2 mmol). After stirring for 10 min at room temperature the solution was diluted with aq.$NaHCO_3$, the aqueous layer separated, and the organic layer washed with water (x3) then brine and then dried over $MgSO_4$. Evaporation of the solvent left an oil which was purified by flash chromatography eluting with 20-40% EtOAc in light petroleum ether. The product diastereomers were just separable under these conditions, with the minor diastereomer **75** eluting first to give a yield of 18% (30 mg) followed by the major diastereomer **74** in 50% (85 mg) yield. TLC EA:LP 1:1 Rf=0.43, 0.29. **^{1}H NMR** (300 MHz, CD_3CN): □□ **Isomer 75**: 7.29, 4H, m, ArH; 7.22, 1H, m, ArH; 5.17, 1H, dd, J=6.5, 8.4 Hz; 5.08, 1H, m; 3.65, 3H, s, OCH_3; 3.61, 1H, dd, J=11.4, 15.6 Hz; 3.27, 1H, ddd, J=1.5, 5.7, 15.9 Hz; 3.12, 1H, dd, J=4.5, 14.3 Hz; 2.98, 1H, bm; 2.72, 1H, m; 2.64, 1H, dd, J=9.9, 14.3 Hz; 2.57, 1H, bm; (2.17, H_2O); 1.68, 3H, m; 1.60, 1H, m, Leu□; 1.36, 9H, s, Boc; 1.16, 1H, m; 0.95, 3H, d, J=6.4 Hz, Leu□; 0.93, 3H, d, J=6.6 Hz. **Isomer 74**: 7.29, 4H, m, ArH; 7.22, 1H, m, ArH; 5.11, 1H, dd, J=5.6, 9.4 Hz; 4.29, 1H, br, NHBoc; 3.81, 1H, dd, J=4.6, 9.8 Hz; 3.65, 3H, s, OCH_3; 3.59, 1H, dd, J=10.8, 15.2 Hz; 3.19, 1H, dd, J=5.5, 15.2 Hz; 3.13, 1H, dd, J=4.5, 13.8 Hz; 2.94, 2H, m's; 2.71, 1H, m; 2.64, 1H, dd, J=10.3, 13.3 Hz; (2.17, H_2O); 1.76, 1H, m; 1.69, 2H, m; 1.57, 2H, m; 1.36, 9H, s, Boc; 0.93, 6H, d, J=6.5 Hz. **^{13}C NMR** (75 MHz, $CDCl_3$): □ Isomer **75** (5S): 175.2; 172.5; 155.9; 138.9; 129.3; 128.5; 126.4; 79.2; 60.91; 60.62; 55.65; 52.19; 45.70; 43.98; 38.12; 37.99; 33.46; 28.30, Boc; 25.01; 23.10; 21.93. Isomer **74** (5R): 175.1; 172.5; 155.7; 139.3; 129.3; 128.7; 126.8; 78.9; 56.01; 55.80; 53.05; 52.14; 42.07; 40.70; 38.01; 37.98; 31.51; 28.26, Boc; 25.03; 23.11 21.74. Mass Spectrum (ISMS) m/z 462.3 (MH^+), calculated for $C_{32}H_{45}N_3O_5$: 461 fragments (OR 70): 406.2 (-tBu).

Example (D). *Selective synthesis of the 3(S), 5(S) diastereomer **75** by the short method*

The 3(S)5(S) diastereomer, the minor product formed as described above, can be selectively synthesised by the use of an intramolecular reductive amination-cyclisation as described below:



Preparation of acyl fluoride **76**:

Z-phenylalanine acid fluoride was prepared by general literature methods (Carpino *et al.*, 1990; Wenschuh *et al.*, 1994) as follows: 1.1 equivalents of diethylaminosulfurtrifluoride (DAST) were added to ZPheOH in dry dichloromethane solution under nitrogen at 0°C. After stirring for 15 min the reaction was worked up by pouring onto iced water and separating the organic layer, washing once with cold water and then drying over $MgSO_4$. The product was purified by precipitation from ether/petroleum ether and dried *in vacuo*. **^{1}H NMR** (300 MHz, $CDCl_3$): □ 7.36, 8H, m's; 7.28, 2H, m; 5.30, 1H, bd; J=7.5 Hz, NH; 5.13, 2H, s, OCH_2Ph; 4.85, 1H, m, □H; 3.20, 2H, m, □H_2. **^{13}C NMR** (75 MHz, $CDCl_3$): □ 161.8, d, $^1J_{CF}$=370 Hz; 155.5; 135.7; 134.2; 129.1; 129.0; 128.5; 128.3; 128.1; 127.7; 67.36; 53.50, d, $^2J_{CF}$=59 Hz; 36.70.

Preparation of **77**:

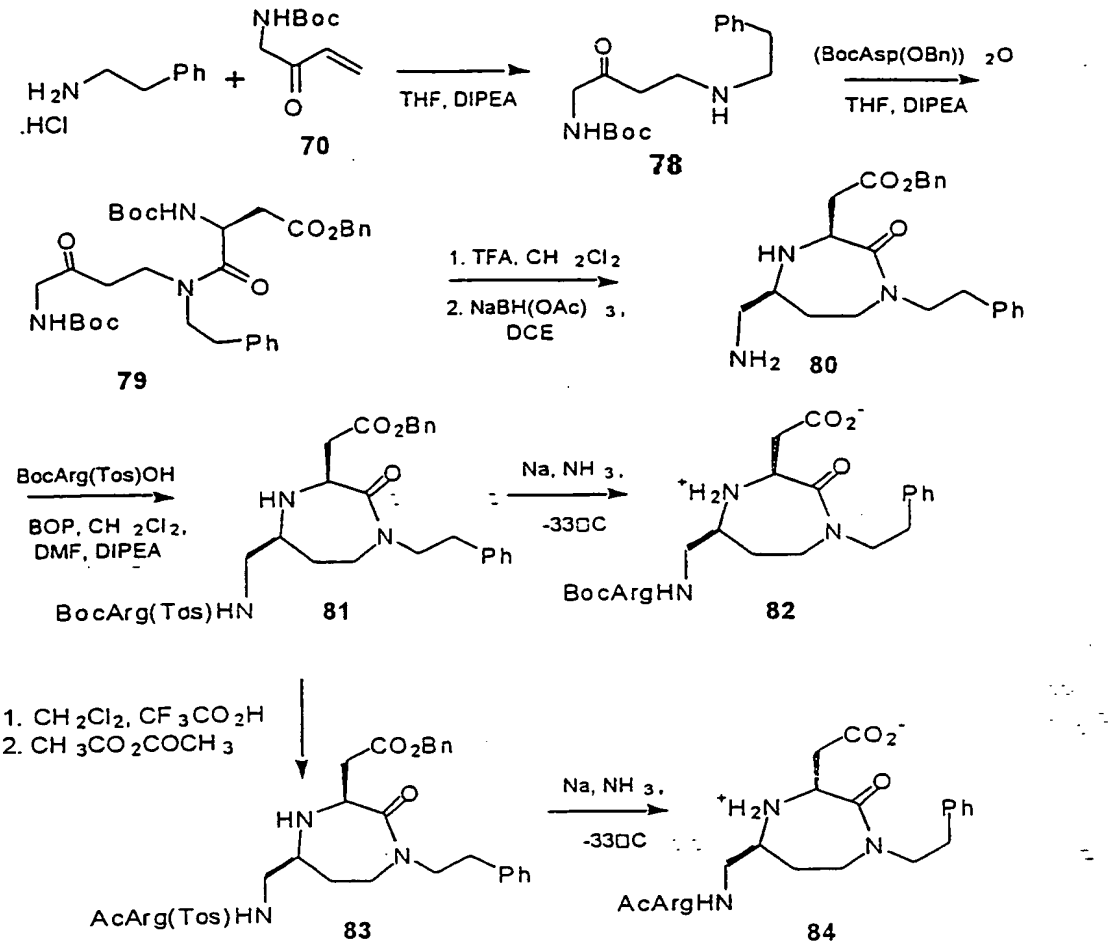
To the amine **71** (2.7 g, 8.2 mmol) dissolved in CH_2Cl_2 (40 mL) was added Z-phenylalanine acid fluoride **76** (prepared as described above) (3.0 g, 10 mmol) and DIEA (1.3 g, 10 mmol) and the solution stirred at room temperature under nitrogen for 30 h. The solvent was then evaporated *in vacuo* and the residue dissolved in ether and

extracted in turn with 1M HCl (x2), 10% aq. Na_2CO_3 (x2), then brine and then dried over $MgSO_4$. The solution was filtered and the solvent removed *in vacuo*. The resulting oil was purified by flash chromatography eluting with 20-40% ethyl acetate in light petroleum ether for a yield of about 80% of the target **77** as a clear oil. TLC 40%EA:LP Rf=0.40. **^{1}H NMR** (300 MHz, $CDCl_3$): □ 7.41-7.13, 10H, Ar; 5.48, 1H, bd, J=9.2 Hz, NHCbz; 5.19, 1H, bm, NHBoc; 5.09, 2H, s, OCH_2Ph; 4.76, 1H, dt, J=6.4, 8.9 Hz, Phe□; 4.38, 1H, dd, J=5.2, 9.3 Hz, Leu□; 3.92, 2H, d, J=4.5 Hz, Gly□; 3.60, 3H, s, OCH_3; 3.54, 1H, m; 3.38, 1H, m; 3.08, 1H, dd, J=8.4, 13.3 Hz; 2.93, 1H, dd, J=6.1, 13.1 Hz; 2.65, 2H, m; 2.80, 1H, m; 2.64, 1H, m; 1.46, 9H, s, Boc; ~1.38, 1H, m; 0.90, 6H, 2xd, J=6.6, 6.5, Leu□. **^{13}C NMR** (75 MHz, $CDCl_3$) amide rotamers (~5:1): only the major peak of rotamer peak pairs is reported: □ 204.1; 172.1; 171.4; 156.7; 155.6; 136.2; 135.8; 129.4-127.1: ArCH; 79.8; 66.82; 58.15; 52.25; 52.05; 50.28; 41.32; 39.58 (2 coincident signals as determined by relative intensity, shift and the presence of both minor rotamer peaks); 37.82; 28.23, Boc; 24.67; 23.08; 21.67. Mass Spectrum (ISMS) m/z 612.3 ($M+H^+$), calculated for $C_{33}H_{45}N_3O_8$: 611; fragments: (OR 60): 556.3 (-tBu); 512.3 (-Boc).

Selective preparation of **75** from **77**:

The ketone **77** (1mmol) was dissolved in 0.1M methanolic HCl (30ml) and 10% palladium on activated carbon (200mg) was added. The solution was hydrogenated at 30 psi H_2 (room temperature) for 8 h and then diluted with aq. $NaHCO_3$ and extracted with ethyl acetate. The organic layer was washed with water (x2) and then brine then dried over $MgSO_4$. Filtration and removal of solvent in vacuo left the crude product **75** in good yield and purity. Analysis of the crude product by NMR and by TLC did not reveal any of diastereomer **74**. The reaction was estimated to be >95% stereoselective.

Example (E). *Synthesis of a biologically active □-turn mimetic for the Arg-Gly-Asp sequence*



Preparation of **78**:

The □,□-unsaturated ketone **70** (1.0 g, 5.4 mmol, prepared as previously described) was reacted with phenethylamine hydrochloride (1.07 g, 6.8 mmol) and DIEA in THF by the method previously described for the preparation of **71**. The crude product **78** was used without further purification for the next reaction. Mass Spectrum (ISMS) m/z 307.2 (MH^+), calculated for $C_{17}H_{26}N_2O_3$: 306; fragments (OR 60): 250.9 (-tBu).

Preparation of **79**:

To a stirred solution of Boc-aspartic acid □-benzyl ester (3.23 g, 10 mmol) in CH_2Cl_2 (10 mL) was added dicyclohexylcarbodiimide (10 mL of 0.5M solution in CH_2Cl_2) at room temperature. A copious precipitate of dicyclohexylurea soom formed; after 10 min the solution was filtered, and the solvent removed *in vacuo*. The residual oil was

added to a solution of crude **78** (1.3 g) in THF, followed by DIEA (645 mg, 5 mmol), and the solution stirred for 4 h. The reaction mixture was diluted with ether/ethyl acetate and washed with 1M HCl, aq. $NaHCO_3$, water, brine and dried over $MgSO_4$. The crude product was purified by flash chromatography eluting with 30-50% ethyl ether in petroleum ether to give a reasonable yield of **79** (estimated as 80% based on **78**) as a clear oil. **^{1}H NMR** (300 MHz, $CDCl_3$, amide rotamers present): □□ 7.38-7.16, 10H, m, Ar; 5.37, 1H, bd, J=9 Hz, AspNHBoc (minor rotamer 5.33, J=10 Hz); 5.25, m, 1H (Gly NH); 5.10, 2H, m, OCH_2Ph; 4.89, 1H, m; 3.93, 2H, d, J=4.4 Hz, Gly□; 3.67-3.53, 3H, m's; 3.47, 1H, m; 2.95-2.52, 6H, m's (including 2.88, 2H, m; 2.63, 2H, ABX, J=15.8, 7.3, 5.8 Hz, □H_2Asp); 1.44, 18H, multiple singlets, 2xBoc. **^{13}C NMR** (75 MHz, $CDCl_3$): □ (major rotamer only) 204.7; 171.0; 170.3; 155.6; 154.8; 137.7; 135.5; 128.9, 128.6, 128.5, 128.2, 126.6: ArCH; 80.06; 79.73 (2x tBoc); 66.57; 50.55; 50.33; 46.99; 42.24; 37.69 (2 signals); 35.50; 28.22 (2x Boc). Mass Spectrum (ISMS) m/z 612.3 (MH^+), calculated for $C_{33}H_{45}N_3O_8$: 611 fragments (OR 60): 556.1 (-tBu); 512.1 (-Boc).

Preparation of **80**:

The ketone **79** (390 mg, 0.64 mmol) in CH_2Cl_2 (2 mL) was treated with trifluoroacetic acid (2 mL) and the solution stirred for 30 min at room temperature. The volatiles were then removed *in vacuo* and CH_2Cl_2 (3 mL) added and removed *in vacuo* (x2). The residual oil was dissolved in 1,2-dichloroethane (5 mL) and $NaBH(OAc)_3$ (270 mg, 1.3 mmol) added. The mixture was stirred for 20 min then the solvent removed and the residue dissolved in ethyl acetate and washed with aq. Na_2CO_3 and then brine and then dried over $MgSO_4$. The crude product **80** (after solvent removal 210 mg, 84%) was of good purity by MS and NMR, with only one diastereomer observed (>95% diastereoselectivity). **^{1}H NMR** (300 MHz, $CDCl_3$): □ 7.39-7.10, 10H, m, Ar; {5.20, 5.16, 5.14, 5.10}, 2H, ABq, J=12.5 Hz) OCH_2Ph; 3.86, 1H, t, J=6.3; 3.76-3.43, 3H, m's; 3.14, 1H, bdd, J=15, 5 Hz; 2.98-2.76, 5H, e; 2.70, 1H, dd, J=7.4, 16 Hz; 2.46, 1H, m; 1.64, 1H, bm; 1.06, 1H bm. **^{13}C NMR** (75 MHz,

$CDCl_3$): □ 173.9; 172.0; 138.9; 135.9; 128.7, 128.4, 128.0, 126.3: Ar; 66.16; 60.49; 56.55; 51.24; 48.39; 45.14; 38.05; 34.15; 33.01. Mass Spectrum (ISMS) m/z 396.2 (MH^+), calculated for $C_{23}H_{29}N_3O_3$: 395.

Preparation of **81**:

The crude amine product **80** (140 mg, ~0.35 mmol) was coupled with BocArg(Tos)OH (182 mg, 1.2 eq) using the BOP reagent (188 mg) and DIEA (55 mg) in DMF/CH_2Cl_2 (5ml). The CH_2Cl_2 was evaporated *in vacuo* and the residue partitioned between diethyl ether/ethyl acetate and aq. $NaHCO_3$. The aqueous layer was separated and the organic layer washed in turn with 1M HCl (x2), water (x2), aq. $NaHCO_3$, brine, and then dried over $MgSO_4$. Filtration and removal of the solvent *in vacuo* left the crude product amide **81** which was purified by flash chromatography eluting with 5-10% ethanol in ethyl acetate (yield 260 mg, 90%). TLC 10% EtOH in EtOAc Rf=0.38. **^{1}H NMR** (300 MHz, CD_3OD): □ 7.74, 2H, d, J=7 Hz; 7.4-7.15, 12H, m's; 5.15, 2H abq, J=11 Hz, OBn; 4.26, 1H, m; 4.03, 1H, m; 3.73, 2H, m; 3.48-3.07, 7H, e; 3.07, 1H, m; 2.92-2.73, 3H, m's; 1.92, 1H, m; 1.73, 1H, m; 1.66-1.45, 4H, e; 1.42, 9H, s, Boc. **^{13}C NMR** (75 MHz, CD_3OD): □ 176.1; 172.5; 172.0 (br); 158.8; 158.1; 143.7; 142.2; 140.3; 137.5; 130.4; 130.1; 129.72; 129.68; 129.4; 128.4; 127.6; 127.3; 127.2; 80.92 (t); 67.75 (CH_2); 62.55 (CH); 57.27 (CH); 56.00 (CH); 52.55 (CH_2); 48.74 (CH_2); 44.42 (CH_2); 41.22 (br, CH_2); 37.00 (CH_2); 35.10 (CH_2); 32.41 (CH_2); 30.15 (CH_2); 28.87 (Boc CH_3); 27.24 (br, CH_2); 21.57 (CH_3). Mass Spectrum (ISMS) m/z 806.4 (MH^+), calculated for $C_{41}H_{55}N_7O_8S$: 805.

Preparation of **82**:

The amine **81** (50 mg, 0.06 mmol) in THF (0.6 mL) was cooled in a dry ice acetone bath and ammonia gas added until ~30 mL of ammonia had condensed. Small pieces of sodium metal (3-6 mg) were added until the blue colour persisted. The reaction was quenched by the addition of ammonium carbonate (25 mg), the dry ice bath removed and the solvent allowed to evaporate at room temperature. The residue (which gave a crude mass spectrum with the product mass as the only

significant peak) was purified by reversed phase HPLC (Vydac C18) eluting with 85% solvent A (=0.1% CF_3COOH in H_2O):15% solvent B (=0.1% CF_3COOH and ~10% H_2O in CH_3CN) for 2 minutes followed by a 2%/min gradient. Only one product diastereomer was observed in the HPLC traces. Mass Spectrum (ISMS) m/z 562.3 ($M+H^+$), calculated for $C_{27}H_{43}N_7O_6$.

Preparation of **83**:

The amine **81** was dissolved in CH_2Cl_2/CF_3CO_2H (2ml, 1:1) and stirred at room temperature for 30 minutes after which the Boc group had been removed. 10ml of CH_2Cl_2 was then added and the volatiles removed in vacuo (repeat once). The residue was again dissolved in CH_2Cl_2 and acetic anhydride (2 eq.) added along with diisopropylethylamine (DIEA, 5 eq.), and the reaction stirred at room temperature for 2 h. The volatiles were removed *in vacuo* and the residue dissolved in ethyl acetate and washed with aq. $NaHCO_3$ then brine and then dried over $MgSO_4$. Filtration and removal of the solvent *in vacuo* left the crude product **83** as an oil in reasonable purity. The ^1H NMR was badly broadened in common solvents at room temperature. ^{13}C NMR (75MHz, $CDCl_3$): □ 173.7; 172.4; 171.9; 171.0; 157.0; 142.1; 140.4; 138.8; 135.8; 129.2, 128.7, 128.4, 128.1, 128.0, 126.3, 125.8: ArCH; 66.22, OCH_2Ph; 60.08, CH; 56.09, CH; 52.94, br, CH; 51.06, CH_2; 48.21, CH_2; 44.31, CH_2; 40.13, br, CH_2; 37.79, CH_2; 34.16, CH_2; 32.97, CH_2; (29.59, 29.50) 1C, br, CH_2; 25.64, br, CH_2; 22.91, CH_3; 21.32, CH_3. Mass Spectrum (ISMS) m/z 748.2 (MH^+), calculated for $C_{37}H_{49}N_7O_7S$: 747.

Preparation of **84**:

Compound **84** was prepared from **83** by dissolving metal reduction as described for the preparation of **82** above. Purification was carried out by HPLC under the same conditions as for **82**.

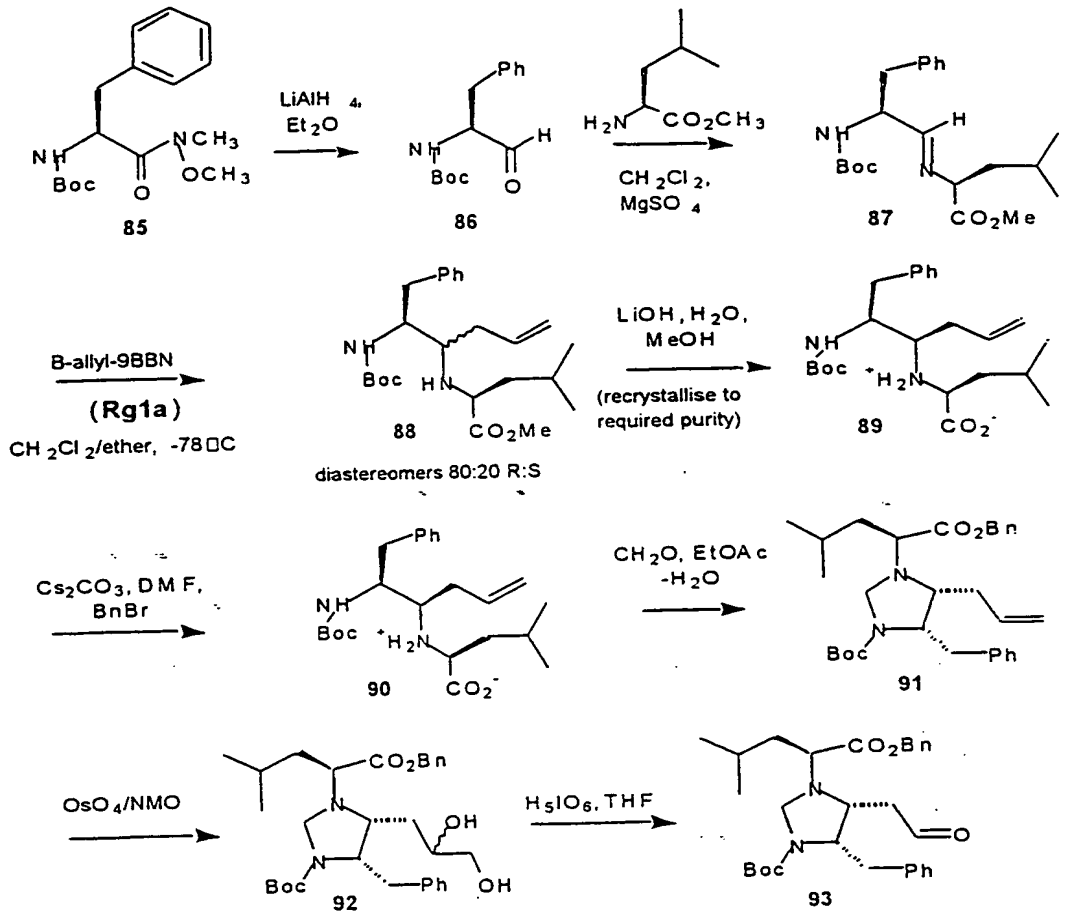
Testing of Arg-Gly-Asp mimetics 82 and 84 for inhibition of platelet aggregation in human platelet rich plasma (PRP)

The peptide sequence arginine-glycine-aspartic acid (RGD) is important to the binding of proteins to certain integrin receptors, such as the $GP_{IIb-IIIa}$ receptor found on the surface of platelets. Several cyclic peptides having the RGD sequence have been found to antagonise the binding of plasma proteins to the $GP_{IIb-IIIa}$ receptor, thereby inhibiting blood clotting. $GP_{IIb-IIIa}$ antagonists have therapeutic potential as anti-thrombotics, there are several in early clinical trials(Humphries, Doyle *et al.*, 1994). Mimetics based on □-turn structures centred on the Asp residue have been successful, this structure was chosen to test the compounds of the invention.

Solutions of the compounds to be tested were made up in water. Platelet aggregation induced by adenosinediphosphate (ADP, 10□M) in human PRP was measured by the decrease in light scattering on aggregation, measured with a platelet aggregometer. The tetra-peptide Ac-Arg-Gly-Asp-Ser-NH_2 was used as a positive control.(Callahan *et al.*, 1992) Compounds **82** and **84** were both found to inhibit platelet aggregation in a dose dependent manner, and both exhibited stronger inhibition than the control peptide. Compound **84** was the strongest, having inhibitory activity approximately five times more potent than Ac-Arg-Gly-Asp-Ser-NH_2 under the conditions of the test.

Example (F). *Synthesis of fully substituted □-turn mimetics for the Phe-Leu-Ala sequence in both the 4(R) and 4(S) configurations*

The synthesis up to the final common intermediate for the 4(R) and 4(S) diastereomers, the aldehyde **93**, is summarised below:-



Bocphenylalanine N,O-dimethylhydroxylamide **85** was synthesised by the general solution phase coupling procedure as previously described from Boc-phenylalanine and N,O-dimethyl hydroxylamine hydrochloride. Yield: ~quantitative. Purification: on a short silica column eluting with ether. **^{1}H NMR** (300 MHz, $CDCl_3$): □ 7.33-7.12, 5H, m, Ar; 5.20, 1H, bd, J~7 Hz, NH; 4.95, 1H, bm, Phe□; 3.66, 3H, s, OCH_3; 3.17, 3H, s, NCH_3; 3.06, 1H, dd, J=6, 13.5 Hz, Phe□; 2.88, 1H, dd, J=7.5, 13.5 Hz; 1.40, 9H, s, Boc. **^{13}C NMR** (75 MHz, $CDCl_3$): □ 172.2; 155.1; 136.5; 129.4; 128.2; 126.7; 79.5; 61.4; 51.4; 38.8, Phe□; 32.0; 28.2, Boc.

The amide **85** was reduced to Bocphenylalanine aldehyde **86** by the method of Fehrentz and Castro (Fehrentz and Castro, 1983) Briefly: amide (2 mmol) dissolved in dry ether (20 mL) and cooled and in

an ice bath under nitrogen, then $LiAlH_4$ (95 mg, 2.5 mmol) added and stirring continued 15 min. Then $KHSO_4$ (477 mg, 3.5 mmol) in 10 mL water added and then 150 mL ether and wash with 1M HCl (cold) (x3), aq. $NaHCO_3$, brine, and dried over $MgSO_4$. Removal of the solvent left the solid aldehyde in ~90% crude yield containing some of the overreduced alcohol as the only significant impurity. TLC EtOAc:light pet. Rf=0.5. **^{1}H NMR** (300 MHz, $CDCl_3$): □ 9.63, 1H, s, aldehyde; 7.37-7.13, 5H, m, Ar; 5.07, 1H, bs, NH; 4.43, 1H, m, Phe□; 3.11, 2H, d(AB) Phe□; 1.43, 9H, s, Boc. **^{13}C NMR** (75 MHz, $CDCl_3$): □ 199.4, aldehyde; 155.3, carbamate; 135.7, ipso; 129.3, 128.7, 127.1: ArCH; 80.2, tBoc; 60.8, Phe□; 35.5, Phe□; 28.2, Boc

Methyl leucinate hydrochloride (0.80 g, 4.4 mmol) was neutralised with 10% aq. Na_2CO_3 solution (25 mL), and the solution was mixed with brine (25 mL) and extracted with CH_2Cl_2 (3x20 mL). The organic extracts were dried over $MgSO_4$ and most of the solvent removed under vacuum (~2 mL residue). This solution of methyl leucinate was added to Boc phenylalanine aldehyde **86** (1.1 g, 4.4 mmol) in CH_2Cl_2 (5 mL), the stirred solution soon became turbid due to the separation of water, dried $MgSO_4$ (500 mg) was added and the solution cleared. After 30 min the solution was filtered into a dried flask under nitrogen. NMR analysis showed that all the aldehyde had been converted to the imine **87** and that significant racemisation had not taken place. The imine was used without further purification for the allylation reaction. **^{1}H NMR** (300 MHz, $CDCl_3$): □ 7.61, 1H, d, J=1.3 Hz, imine; 7.32-7.14, 5H, m, Ar; 5.69, 1H, bd, J=4.5 Hz, NH; 4.49, 1H, m, Phe□; 3.85, 1H, dd, J=5.5, 8.5 Hz, Leu□; 3.69, 3H, s, OCH_3; 3.20, 1H, dd, J=5.0, 14.5 Hz, Phe□; 2.96, 1H, dd, J=8.0, 13.5 Hz; Phe□; 1.63, 1H, m; 1.46, 9H, s, Boc; 1.42, 1H, m; 1.30, 1H, m; 0.88, 3H, d, J=6.5 Hz, Leu□; 0.80, 3H, d, J=6.5 Hz, Leu□. **^{13}C NMR** (75 MHz, $CDCl_3$): □ 171.7, ester; 164.3, CH, imine; 154.6, carbamate; 136.1, ipso; 128.9, 127.7, 126.0: ArCH; 78.56, tBoc; 69.51; 54.08; 51.32; 41.02, CH_2; 38.04, CH_2; 27.73, Boc; 22.35; 22.48; 20.63.

B-allyl-9-borabicyclononane **Rg1a** can be synthesised from B-methoxy-9-borabicyclononane (synthesised in turn from the methanolysis of 9-BBN (Kramer and Brown, 1974)) by the method of Kramer (Kramer and Brown, 1977). Alternatively the following one-pot synthesis from 9-BBN was used: a suspension of 9-BBN (crystalline dimer, 8.97 g, 73.5 mmol) in anhydrous ether (75 mL) was stirred under nitrogen and cooled to 0°C. Methanol (3.3 mL, 81 mmol) was slowly added by syringe (gas evolved), and vigorous stirring continued for ~3 h (9-BBN gradually dissolves, gas evolution ceases). Allylmagnesium bromide in ether (81 mL of a 1.0M solution) was slowly added to the solution (still cooled to 0°C); (a thick grey ppt. forms, stirring may be difficult). Stirring was continued for 1 h then the solution was allowed to warm to room temperature and the ether was pumped off under moderate vacuum (~300->20mbar). The residue was re-suspended in anhydrous hexane (100 mL) and then stirring stopped to allow the magnesium salts to settle out. The solution was estimated by reaction with a known amount of methylphenylketone in ether (found to be ~0.57M, equal to 78% yield). The clear solution of B-allyl-9-BBN was used directly for allylation of the imines. (This procedure was adapted from one described by Rachlera and Brown (Racherla *et al.*, 1992)) The imine **87** (~23 mmol) was dissolved in dry diethylether (100 mL) under nitrogen and the stirred solution cooled to -78°C. B-allyl-9-BBN (47.5 mL of ~0.57M solution in hexane, ~27 mmol) was added and the solution stirred for 1 h and then allowed to warm to room temperature with stirring for an additional 1 h. Glacial acetic acid (1.5 mL) was added and the ether was removed *in vacuo*. The residue was dissolved in acetonitrile (100 mL) and more glacial acetic acid (5 mL) added. The solution was then refluxed until all of the borane adduct had been converted to the amine (~24 h, monitored by TLC: Rf adduct>Rf amine = 0.32 in 1:5 EtOAc:light pet.). The acetonitrile was removed *in vacuo* and the residue partitioned between ether/light petroleum and 10% aq. Na_2CO_3. The organic layer was washed again with 10% aq. Na_2CO_3 and then extracted with a solution of

25% methanol in 0.5M HCl (three times), the organic layer containing the neutral reaction products (~6 g) was discarded. The aq. acid extracts were immediately neutralised with solid $NaHCO_3$ and then extracted with ether. The ether solution was washed with water then brine and then dried over $MgSO_4$. Evaporation of the solvent left the amine products (5.9 g) which were further purified by flash chromatography eluting with 7.5-15% ethyl acetate in light petroleum for a yield of 50+% of the amines **88** based on the crude aldehyde **86** used in the imine formation. Some separation of the diastereomers was observed in the chromatography, but they were not well resolved. Alternatively the crude amines were hydrolysed to the amino acid as described below and purified by recrystallisation. **^{1}H NMR** (300 MHz, $CDCl_3$), major diastereomer: □ 7.32-7.13, 5H, m, Ar; 5.84, 1H, m, vinylCH; 5.11, 2H, m, vinylCH_2; 5.00, 1H, d, J=8 Hz, NHBoc; 3.88, 1H, m, Phe□; 3.66, 3H, s, OCH_3; 3.40, 1H, t, J=7 Hz, Leu□; 2.87, 1H, dd, J=5, 13 Hz, Phe□; 2.69, 2H, m's: Phe□+CH(homoallyl); 2.23, 2H, m, allyl; 1.7, 1H, b, NH(amine); (1.65, 1H, m; 1.47, 2H, m) Leu□+□; 1.33, 9H, s, Boc; 0.90, 6H, t(2 doublets) J=7, 7 Hz, Leu□. **^{13}C NMR** (75 MHz, $CDCl_3$), major isomer: □ 176.1; 155.4; 138.6, ipso; 135.2, CH vinyl; 129.2, 128.2, 126.1: CHAr; 117.4, CH_2 vinyl; 78.8, tBoc; 58.94; 58.56; 54.10; 51.71; 42.87; 36.52; 35.61; 28.24, Boc; 24.78; 22.68; 22.23. Mass Spectrum (ISMS) m/z 419.2 (MH^+), calculated for $C_{32}H_{45}N_3O_5$: 418 fragments (OR 65): 363.2, (-tBu).

The crude amine product **88** (1.7 g, ~4 mmol) was dissolved in methanol/water and $LiOH.H_2O$ (800 mg, 19 mmol) added. The solution was stirred at room temperature until the hydrolysis was complete (12 h) and then neutralised with 1M HCl (19 mL). On standing a copious white precipitate formed which was filtered off and washed with water. The solid was recrystallised from ethanol-water (~95:5) to give fine needles of (mainly) the major diastereomer **89** (first crop 1 g), m.p.:175-177°C. The product was further recrystallised as required. **^{1}H NMR** (300 MHz, CD_3OD): □ (ref. 3.31 ppm) 7.33-7.18, 5H, m; 5.90, 1H, m; 5.35, 1H, d;

J=17.1 Hz; 5.26, 1H, d, J=10.2 Hz; 4.31, 1H, m; 3.65, 1H, dd, J=5.7, 7.9 Hz; 3.27, 1H, m; 2.92, 1H, dd, J=5.2, 14.0 Hz; 2.76, 1H, dd, J=10.1, 14.0 Hz; 2.59, 1H, m; 1.82, 1H, m; 1.37, 9H, s, (Boc); 0.97, 3H, d, J=7 Hz; 0.94, 3H, d, J=7 Hz. **^{13}C NMR** (75 MHz, CD_3OD): □ (ref. 49.15 ppm) 173.7; 159.4; 138.8; 134.5; 130.33; 129.8; 128.0; 120.5; 81.34; 63.65; 55.84; 41.19; 37.90; 32.70; 28.78; 26.11; 23.56. Mass Spectrum (ISMS) m/z 405 (MH^+), calculated for $C_{23}H_{36}N_2O_4$: 404.

The amino acid **89** was esterified to **90** by the method of Bodansky and Bodansky (Bodansky and Bodansky, 1984) as follows: the amino acid **89** (400 mg, 1 mmol) was dissolved in methanol/water and neutralised with Cs_2CO_3 (300 mg), then the solvents were removed *in vacuo*, then DMF added and removed *in vacuo*. The residue was dissolved in DMF (10 mL) and benzyl bromide (190 mg, 1.1 mmol, purified by passage through a short column of basic alumina) added to the stirred solution. After 2 h the reaction was diluted with aq. $NaHCO_3$ and extracted with 1:1 EtOAc:light pet. The organic layer was washed in turn with aq.$NaHCO_3$, water (x2), brine and then dried over $MgSO_4$. Evaporation of the solvent left the product **90** as a clear oil which solidified to a low melting solid (m.p. ~55°C) on standing (500 mg, ~100%). TLC 25%EtOAc in light pet. Rf=0.57. **^{1}H NMR** (300 MHz, $CDCl_3$): □ 7.38-7.32, 4H, m; 7.28-7.14, 6H, m; 5.82, 1H, m; 5.19-5.05, 4H, m's, (OBn ABq, J=12.5 Hz, □$_a$=5.16, □$_b$=5.12 ppm); 4.9, 1H, br; 3.88, 1H, br; 3.44, 1H, bt, J=7 Hz; 2.88, 1H, dd, J=5, 14 Hz; 2.77-2.60, 2H, bm; 1.63, 1H, m; 1.56-1.35, m, 2H; 1.33, 9H, bs (Boc); 0.88, 3H, d, J=6.5 Hz; 0.85, 3H, d, J=6.5 Hz. **^{13}C NMR** (75 MHz, $CDCl_3$): □ 175.5; 155.5; 138.6; 135.8; 135.2; 129.2; 128.5; 128.2; 126.1; 117.4; 78.90; 66.40; 58.96; 58.49; 54.25; 42.83; 36.33; 35.71; 28.27 (Boc); 24.77; 22.63; 22.32. Mass Spectrum (ISMS) m/z 495 ($M+H^+$), calculated for $C_{30}H_{42}N_2O_4$: 494.

The amine **90** (500 mg, 1 mmol) was dissolved in ethyl acetate (20 mL) and 37% aqueous formaldehyde solution (0.5 mL) was added. The solution was stirred for 12 h and then diluted with light

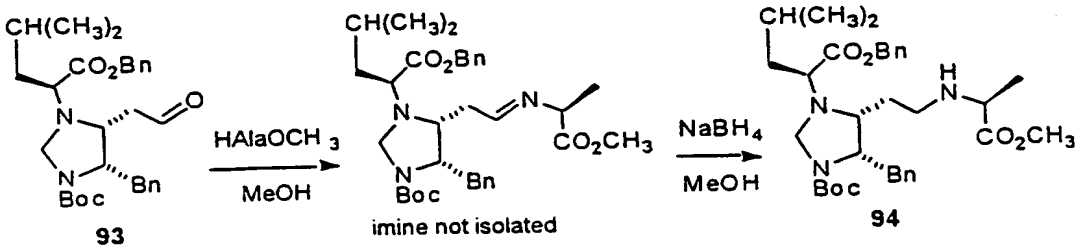
petroleum (40 mL) and washed in turn with aq. $NaHCO_3$, water (x2) and brine and then dried ($MgSO_4$). Removal of the solvent *in vacuo* gave the product **91** as a clear oil in approximately quantitative yield. Further purification was carried out by flash chromatography eluting with 10% ethyl acetate in light pet. **^{1}H NMR** (500 MHz, CD_3CN): □□ (rotamers were present in a ratio of 7:3) 7.36, 4H,m, Ar; 7.27-7.11, 6H, Ar; 5.70, 1H, m, vinyl CH; 5.17-4.97, 4H, m's, vinyl CH_2 and OCH_2Ph; 4.44, 0.7H, d, J=5.0 Hz, ring CH_2(a), major rotamer; 4.33, 0.3H, d, J=4.4 Hz, ring CH_2(a), minor rotamer; 4.19, 0.7H, d, J=5.0 Hz, ring CH_2(b), major rotamer; 4.09, 0.3H, d, J=4.6 Hz, ring CH_2(b), minor rotamer; 4.06, 0.3H, m, Phe□, minor; 4.02, 0.7H, m, Phe□, major; 3.74, 0.7H, dd, J=9.8, 6.0 Hz, and 3.69, 0.3H, m, Leu□; 3.10, 1H, m, ring methine (homoallyl); 2.88, 0.3H, m, Phe□(a); 2.84, 0.7H, dd, J=4.1, 13.4, Phe□(a); 2.72, 0.3H, dd, J=6.5, 13.5, Phe□(b); 2.65, 0.7H, dd, J=9.5, 13.2, Phe□(b); 2.49, 1H, m, allyl(a); 2.15, 1H, m, allyl(b); 1.76-1.42, 3H, m's, Leu□+□; 1.33, 2.5H, s, Boc, minor rotamer; 1.09, 6.5H, s, Boc, major rotamer; 0.97-0.84, 6H, d's, Leu□ (major rotamer: 0.94, J=6.3 Hz; 0.90, J=6.2 Hz). **^{13}C NMR** (75 MHz, CD_3CN), only major rotamer reported except where indicated: □ (ref. 118.69 ppm) 173.3; 154.2; 140.9; 137.8; 136.3 (CH); 131.3; 129.9; 129.7; 129.6; 129.5; 127.2; 118.2 (CH_2); 79.98 (Boc tertiary); 67.17 (CH_2); 63.49 (CH); 62.47 (CH_2); 60.91 (CH); 57.68 (CH); 40.34 (CH_2); 36.04 (CH_2); 33.18 (CH_2); (29.08 Boc minor rotamer); 28.61 (Boc major rotamer); 25.98 (CH); 23.79 (CH_3); 22.36 (CH_3). Mass Spectrum (ISMS) m/z 507 (MH^+), calculated for $C_{31}H_{42}N_2O_4$: 506.

The alkene **91** was dihydroxylated with OsO_4/N-methylmorpholine-N-oxide in tBuOH/water as previously described for the dihydroxylation of **60**. The crude product **92** was used directly in the next reaction. TLC 1:1 EtOAc:light pet. Rf=0.36. Mass Spectrum (ISMS) m/z 541 ($M+H^+$), calculated for $C_{31}H_{44}N_2O_6$: 540.

The glycol **92** (87 mg, 0.16 mmol) was dissolved in THF (4 mL) and H_5IO_6 (37 mg, 0.16 mmol) dissolved in THF (3 mL) was added

and the reaction stirred at room temperature. A precipitate of iodic acid rapidly formed and the reaction was complete in <5 min. The THF solution was diluted with ether and washed in turn with 10% aq.Na_2CO_3, water, brine and then dried ($MgSO_4$). The product aldehyde **93** was of good purity but was not particularly stable to storage. Any traces of acid must be rigorously excluded to prevent isomerisation to the trans isomer. A portion was purified by flash chromatography, eluting with 15%EtOAc in light petroleum. TLC 15%EtOAc in light pet. Rf=0.27. The yield was good (>80%). Amide rotamers were evident in the NMR spectra, ratio ~3:1, only the peak due to the main rotamer is reported unless otherwise noted. **^{1}H NMR** (300 MHz, CD_3CN, ref 1.94 ppm): □ 9.53, 1H, s; 7.42-7.10, 10H, m's; 5.11, 2H, s, (OCH_2Ph); 4.41, 1H, br; 4.25, 1H, q, J=6.3 Hz; 4.15, 1H, br; 3.56, 1H, dt, J=8.5, 5.7 Hz; 3.54, 1H, bm; 2.90-2.58, 4H, m; 1.75-1.45, 3H, bm; 1.37, bs, Boc minor rotamer; 1.20, bs, Boc major rotamer; 0.92, 3H, d, J=6 Hz; 0.88, 3H, d, J=5.7 Hz. **^{13}C NMR** (75 MHz, CD_3CN, ref 118.69 ppm): □ 202.0; 173.1; 154.2; 140.4; 137.6; 131.1; 129.9; 129.62; 129.55; 127.26; 80.28 (Boc tertiary); 67.31 (CH_2); 61.90 (CH_2); 60.43 (CH); 58.56 (CH); 57.95 (CH); 43.75 (CH_2); 40.36 (CH_2); 36.48 (CH_2); 28.66 (Boc); 25.83 (CH); 23.67 (CH_3); 22.25 (CH_3). Mass Spectrum (ISMS) m/z 509 (MH^+), calculated for $C_{30}H_{40}N_2O_5$: 508.

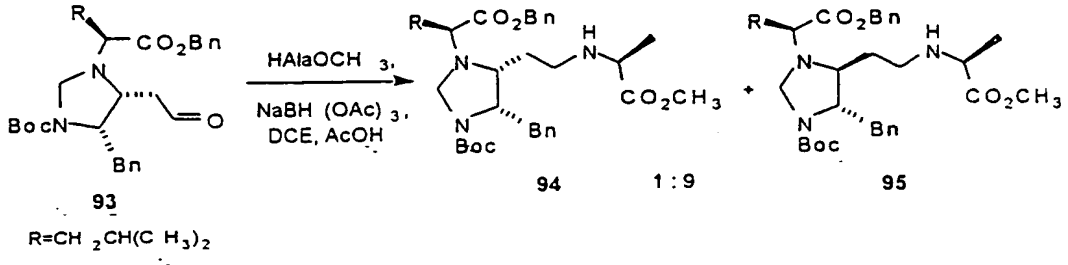
Conversion of 4,5-cis aldehyde **93** to the 4,5-cis 4(S) amine product was completed by a two step reductive amination procedure as illustrated below:



Alanine methyl ester hydrochloride (120 mg, 0.86 mmol) was dissolved in 1:1 brine:10%aq.Na_2CO_3 and extraction into CH_2Cl_2 (x2). The organic extracts were dried ($MgSO_4$), filtered and the majority of the solvent removed *in vacuo* to leave the volatile amine which was added to a solution of the freshly prepared aldehyde **93** (100 mg, 0.2 mmol) dissolved in methanol (~7 mL, strictly acid free). The solution was stirred at room temperature for 2 h whereupon analysis of a test portion reduced with $NaBH_4$ showed imine formation to be complete (none of the alcohol formed on reduction of aldehyde was detected). Solid $NaBH_4$ (50 mg, 1.3 mmol) was added to the solution and stirring continued for 10 min and then the reaction partitioned between ethyl acetate and a water/brine/10%aq.Na_2CO_3 mixture. The aqueous phase was separated and the organic layer washed with water (x2) then brine and then dried ($MgSO_4$). NMR analysis of the crude product failed to detect the corresponding trans (S) diastereomer (<5%). Evaporation of the solvent left an oil which was purified by flash chromatography eluting with 20-40% EtOAc in light petroleum for a 60-70% yield of **94**. TLC 40%EtOAc:light pet. Rf=0.43. Rotamers observed in the NMR spectra, ratio ~3:1, separate signals due to the minor rotamer recorded only where indicated. **^{1}H NMR** (300 MHz, CD_3CN, ref. 1.94 ppm): □ 7.37, 4H, m,; 7.3-7.1, 6H, m; 5.12, 5.09: 2H, ABq, J=12 Hz; 4.39 (major rotamer), 4.29 (minor): 1H, d, J=5 Hz; 4.15, 1H, J=5 Hz; 4.06, 1H, m, PheH□; 3.75-3.57, 4H, m, LeuH□+OCH_3; 3.25-3.10, 1H, m; 3.03, 1H, m; 2.87-2.60, 2H, m, Phe□; 2.52-2.25, 2H, m; 1.81, 1H, m; 1.67, 1H, m; 1.6-1.38, 2H, m; 1.34, bs, Boc minor rotamer; 1.19, m, Ala□; 1.15, bs, Boc major rotamer; 0.93, 3H, d, J=6.6 Hz; 0.89, 3H, d, J=6.3 Hz. **^{13}C NMR** (75 MHz, CD_3CN, ref. 118.69 ppm): □ 177.3; 173.4; 154.2; 141.0; 137.7; 131.2; 130.9; 129.9; 129.7; 129.6; 129.5; 127.1; 80.02 (Boc tertiary); 67.18 (CH_2); 62.55 (CH); 62.25 (CH_2); 60.75 (CH); 57.67 (2xCH, coincident signals); 52.55 (OCH_3); 45.96 (CH_2); 40.96 (CH_2); 36.15 (CH_2); 29.00 (Boc, minor rotamer); 28.73 (CH_2); 28.62 (Boc, major rotamer); 25.96 (CH);

23.66 (CH_3); 22.35 (CH_3); 19.7 (CH_3). Mass Spectrum (ISMS) m/z 596 ($M+H^+$), calculated for $C_{34}H_{50}N_3O_6$: 595.

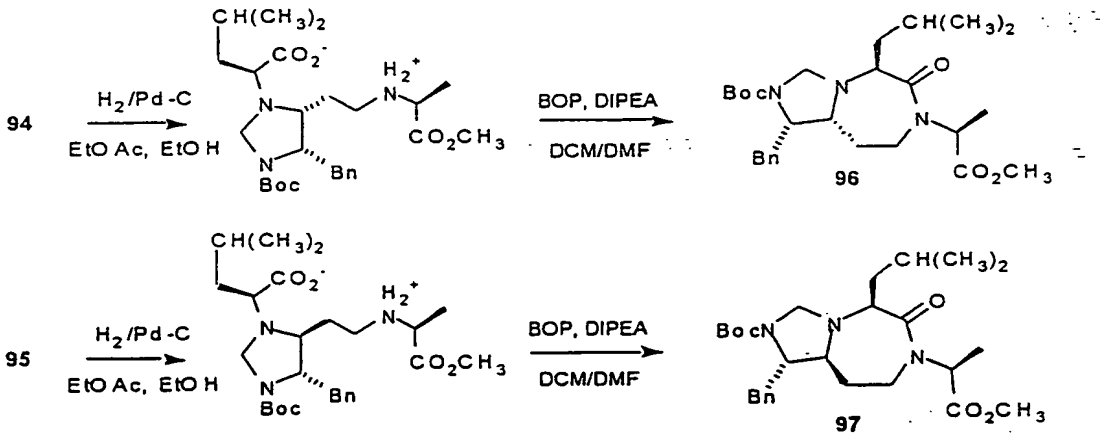
Reductive amination of aldehyde **93** (or the 4,5-trans isomer) with $NaBH(OAc)_3$ in dichloroethane gave rise to a mixture of products **94** and **95** in the ratio 1:9.



The aldehyde **93** (50 mg, 0.1 mmol) was dissolved in 1,2-dichloroethane (5 mL) and alanine methyl ester (~2 equivalents) and acetic acid (1drop, ~14 mg) were added. The mixture was stirred at room temperature for 5 min and then $NaBH(OAc)_3$ (40 mg, 2 eq.) was added and stirring continued for 30 min. The solvent was then removed *in vacuo* and the residue partitioned between EtOAc and 10% aq. Na_2CO_3, the organic layer was washed with water and brine and then dried ($MgSO_4$). The product contained both diastereomers in the ratio ~9:1, trans:cis. The products were purified by flash chromatography eluting with 20-45% EtOAc in light petroleum. TLC 40% EtOAc:light pet. Rf=0.43 (minor diastereomer, **94**, cis), 0.23 (major diastereomer, **95**, trans). Combined yield ~60%. Rotamers were not observed although significant peak broadening was present, as observed for the corresponding trans aldehyde. The configuration of the major product was determined by NMR (NOESY experiment). **^{1}H NMR** (300 MHz, CD_3CN, ref 1.94 ppm): □ 7.24-7.14, 10H, m's; 5.13, 2H, s, OCH_2Ph; 4.38, 1H, br, ring methylene(i); 3.97, 1H, bd, ring methylene(ii); 3.61, 3H, s, OCH_3; 3.75, 1H, ddd, J=2.7, 4.3, 8.7 Hz, PheH□; 3.50, 1H, m, LeuH□; 3.13, 1H, m, PheC'H(ring); 2.97-2.88, 2H, m, AlaH□+PheH□(i); 2.72, 1H, dd, J=2.9, 8.7 Hz, PheH□(ii); 2.33, 1H, ddd, J=11.5, 7.3, 5.5 Hz, CH_2NH(bridge)(i);

1.98, 1H, m (dt, overlaps with solvent peak), CH_2NH(bridge)(ii); 1.53, 2H, m, Leu□+□; 1.43, 9H(s)+1H(m), Boc+Leu□; 1.35, 1H, m, bridge CH_2(i); 1.29, 1H, m, bridge CH_2(ii); 1.06, 3H, d, J=7.0 Hz, Ala□; 0.88, 6H, m, Leu□. **^{13}C NMR** (75 MHz, CD_3CN, ref 118.69 ppm): □ 177.2; 174.6; 154.5; 140.1; 137.6; 131.0; 129.9; 129.7; 129.6; 127.6; 80.61 (Boc tertiary); 67.50 (CH_2); 63.62 (CH_2); 63.5 (CH, br); 62.4 (CH, v.br); 60.67 (CH); 57.70 (CH); 52.47 (CH_2); 45.15 (CH_2); 40.65 (CH_2, v.br); 39.76 (CH_2); 32.81 (CH_2); 29.00 (CH_3, Boc); 26.21 (CH); 23.47 (CH_3); 22.88 (CH_3); 19.62 (CH_3). Mass Spectrum (ISMS) m/z 596 (MH^+), calculated for $C_{34}H_{49}N_3O_6$: 595.

The diastereomeric amines were converted to the protected □-turn mimetic compounds **96** and **97** as described below:



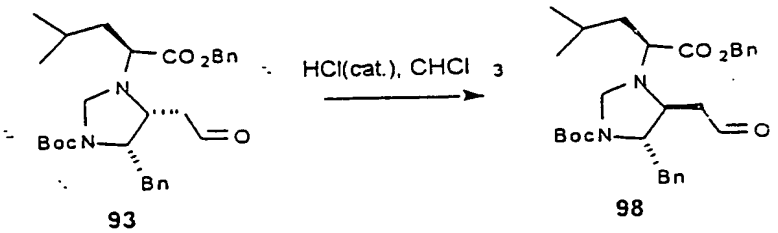
The 4,5-cis amine **94** (42 mg, 0.07 mmol) was dissolved in ethyl acetate:ethanol 10:3 (13 mL) and 35 mg of 10% palladium on activated carbon was added and the mixture hydrogenated at 32 psi H_2 for 3 h to deprotect the benzyl ester to the amino acid (MH^+ = 506 Da). The solution was filtered and the solvent removed *in vacuo*, then the residue was dissolved in DMF (2 mL) and diluted with CH_2Cl_2 (15 mL) and DIEA (50 mg, ~0.4 mmol) and BOP reagent (50 mg, 0.11 mmol) were added to the stirred solution at room temperature. The cyclisation was complete within a few minutes; the CH_2Cl_2 was then removed *in vacuo*

and the residue diluted with ethyl acetate and washed in turn with 10% aq.Na_2CO_3/brine, water (x2), brine and then dried ($MgSO_4$) and the solvent removed *in vacuo* to leave a clear oil which was purified by flash chromatography eluting with 20% EtOAc in light petroleum for a yield of 25 mg (70%) of **96**. TLC 1:1 EtOAc:light pet ~0.45 The NMR spectra in CD_3CN at room temperature were significantly broadened indicating a degree of conformational interconversion slow on the NMR timescale. **^{1}H NMR** (300 MHz, CD_3CN): □ 7.32-7.15, 5H, m, Ar; 4.88, 1H, q, J=7.1 Hz, Ala□; 4.20, 1H, bd, J=4.8 Hz, NCH_2N(a); 4.13, 1H, m, Phe□; 4.09, 1H, bd, J=5.0 Hz, NCH_2N(b); 3.72, 1H, m, Leu□; 3.65, 3H, s, OCH_3; 3.52, 1H, bdd, J=10.6, 15.2 Hz, bridge CH_2CH_2N(a); 3.30-3.21, 2H, m's, CH_2CH_2N(b) and PheC'H; 2.94, 1H, bm, Phe□(a); 2.76, 1H, bm, Phe□(b); 2.25 water peak; 1.9-1.4, 5H, e, Leu□+□ and bridge CH_2CH_2N; 1.29, 3H, d, J=7.1 Hz, Ala□; 3.25, 9H, vbr, Boc; 0.92, 6H, d, J=6.2 Hz, Leu□. **^{13}C NMR** (75 MHz, CD_3CN): □ 173.5 (the amide and ester peaks appear to be co-incident); 154.9 (carbamate, br); 140.7; 130.7 (br); 129.6; 127.3; 80.54; 66.47; 63.83 (br); 62.36; 60.4 (very br); 56.29; 52.97; 44.77; (36.96, 36.40) very br, just resolved; 33.3 (very br); 28.78 (Boc, br); 26.86; 23.90 (br); 22.63; 15.47. Mass spectrum (ISMS) m/z 250.2 ($M+H^+$), calculated for $C_{28}H_{37}N_3O_6$: 511 fragments (OR 60): 441, (-tBu); 397, (-Boc).

The synthesis of **97** was as for **96** but using the trans amine **95**. TLC 1:1 EtOAc:light pet. Rf=0.53. The NMR spectra in CD_3CN were were well resolved and rotamers were present in the ratio of 11:9; signals attributable to the same atom in the different rotamers are placed in parentheses where possible. **^{1}H NMR** (300 MHz, CD_3CN, ref 1.94 ppm): □ 7.34-7.16, 5H, m; 4.69, 1H, m; 4.13, 1H, d, J=4.4 Hz; 3.92, 1H, m; (3.83, d, J=4.4; 3.79, d, J=4.4 Hz), 1H; 3.76-3.60, 2H, m's; (3.61, s; 3.81, s), 3H, OCH_3; 3.26, 1H, m; 3.15, 1H, m; 2.99, 1H, m; 2.77, 1H, m; 1.85-1.49, 3H, m's; (1.44, s; 1.41, s), 9H, Boc; 1.30, 3H, d, J=7.2 Hz, Ala□; 1.36-1.24, 2H, m; 0.98-0.91, 6H, m. **^{13}C NMR** (75 MHz, CD_3CN, ref 118.69 ppm): □ 174.4; 173.3; 154.6; (140.54, 140.49); 130.7;

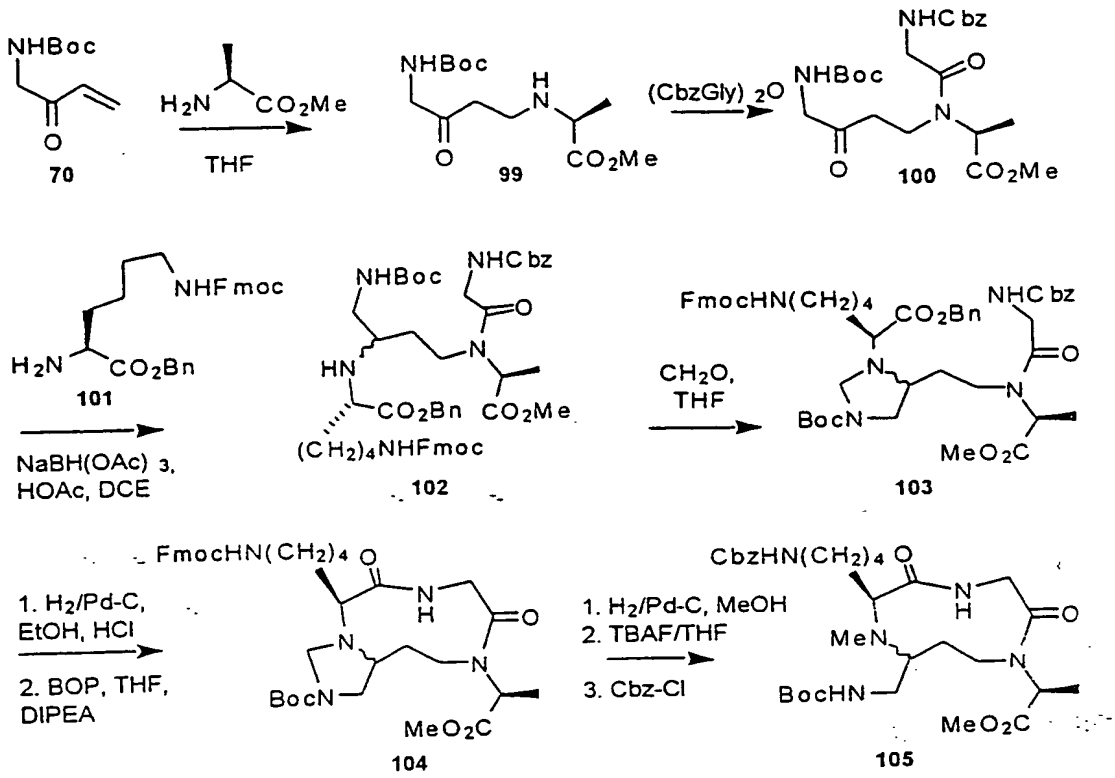
130.6; 129.8; 127.6; (80.65, 80.54), Boc tertiary; (66.12, 65.48, 65.21, 64.90) 2xCH; 60.67, CH_2; (56.82, 56.74), CH; (56.41, 56.24), CH; 52.87, CH_3; (46.19, 46.12), CH_2; (40.72, 39.84), CH_2; 39.16, CH_2; 30.44, CH_2; (29.03, 28.93) Boc; (25.64, 25.58), CH; 24.19, CH_3; 22.43, CH_3; 15.76, CH_3. Mass Spectrum (ISMS) m/z 488 (MH^+), calculated for $C_{28}H_{37}N_3O_6$: 487.

Example (G). *Acid catalysed isomerisation of aldehydes **93***



The trans (4(S)) aldehyde was obtained by the acid catalysed isomerisation of the cis diastereomer **93** in chloroform solution with catalytic HCl present. Significant decomposition to multiple unidentified by-products (most having high Rf) also occurs under the isomerisation conditions. The product was purified by flash chromatography eluting with 15% ethyl acetate in petroleum ether for a yield of about 35% **98** from crude **93**. **^{1}H NMR** (300 MHz, CD_3CN, ref. 1.94 ppm): □ 9.41, t, J=1.8 Hz; 7.45-7.10, 10H, m; 5.12, 2H, m, OCH_2Ph; 4.46, 1H, br; 4.01, 1H, bd; 3.82, 1H, m; 3.62-3.46, 2H, m; 2.95, 1H, bdd, J=13.0, 4.4 Hz; 2.81, 1H, dd, J=13.2, 8.0 Hz; 2.37, 2H, m (ABq of dd, J_{AB}=31, J_{ddA}=4.6, 1.8 Hz; J_{ddB}=7.2, 2.1 Hz), □-aldehyde; 1.75-1.25, 12H, e (1.4, bs, Boc); 0.9, 6H, bm. **^{13}C NMR** (75 MHz, $CDCl_3$): □ 202.9; 174.5; 154.4; 139.7; 137.5; 131.0; 129.9; 129.8; 129.7; 127.7; 80.81; 67.61; 64.03 (br); 63.18 60.49; 59.9 (br); 47.0 (br); 45.95; 39.88; 28.96 (Boc); 26.12; 23.25; 22.97.

Example (H). *Synthesis of a □-turn mimetic **II(i)***



Compound **70** was prepared as described above, and reacted with alanine methyl ester to form **99** using the same method previously described for the synthesis of **71**. The crude amino ketone **99** (1.22g) was reacted with Cbz-glycine symmetric anhydride (synthesised from 1.95g CbzGlyOH and 9.3mls 0.5M dicyclohexylcarbodiimide in dichloromethane) and 0.6g DIEA in dichloromethane. The reaction was stirred at room temperature for 10 hours then diluted with ether (any DCU precipitate was filtered off) and the ether solution was washed with 1M HCl, aqueous sodium bicarbonate then brine and then dried over magnesium sulfate (removed by filtration) and the volatiles removed under reduced pressure to leave the crude product as an oil which was purified by flash chromatography eluting with 2:1 ethyl acetate:light petroleum ether, yield of **100** was 1.8g (90%). Reductive amination of **100** with **101** derived from the deprotection of BocLys(Fmoc)OBn (TFA. CH_2Cl_2) is carried out by the previously described method for the formation of **73** (71% yield after flash chromatography eluting with 2:1 to

3:1 ethyl acetate:light petroleum). The product amine **102** was dissolved in ethyl acetate and formalin added to the stirred solution resulting in the formation of imidazolidine **103**. The ethyl acetate solution was washed with aqueous sodium bicarbonate, water (twice), brine and then dried over magnesium sulfate (removed by filtration) and the volatiles removed under reduced pressure to leave the crude product as an oil which was purified by flash chromatography eluting with 3:2 ethyl acetate:light petroleum ether (yield >75%). The protected pre-cyclisation compound **103** (400 mgs) was dissolved in 0.1M ethanolic HCl (20 mls) and hydrogenated with 250mgs of 10% Pd-C. The hydrogenation was complete after 7 hours (about 40 psi H_2, room temperature). The solution was filtered through a celite pad to remove the catalyst and 50 mls of DMF added. Volatiles (ethanol) were removed under reduced pressure then a solution of BOP reagent (300 mgs) and DIEA (300 mgs) in 150 mls of DMF was added and the mixture stirred at room temperature for 15 minutes. Most of the DMF was removed under reduced pressure and the residue dissolved in ethyl acetate and washed with 1M HCl, aqueous sodium bicarbonate, water (twice), brine and then dried over magnesium sulfate (removed by filtration) and the volatiles removed under reduced pressure to leave about 300 mgs of crude product **104**. The crude product was dissolved in 30 mls methanolic HCl (0.1M) and hydrogenated (200mgs Pd-C, 40psi H_2) for 24 hours reducing the imidazolidine to an N-methyl group. The catalyst was filtered off (celite) and the solvent removed under reduced pressure, the residue was then treated with tetrabutylammonium fluoride in THF to remove the FMOC group. The free amine was then reprotected by addition of benzyl chloroformate (65 mgs) and DIEA (100 mgs). After stirring for 1 hour ethyl acetate was added and the organic layer was washed with 1M HCl, water, then brine, dried over magnesium sulfate (removed by filtration) and the volatiles removed under reduced pressure to leave an oil which was purified by flash chromatography eluting with 3-5% ethanol in chloroform for a yield of about 40% of **105** based on **103**.